



Classic External Radiation Studies and Concepts

John D Boice Jr
International Epidemiology Institute
Vanderbilt University Medical Center
May 17 , 2011

“And it was so typically brilliant of you to have invited an epidemiologist.”

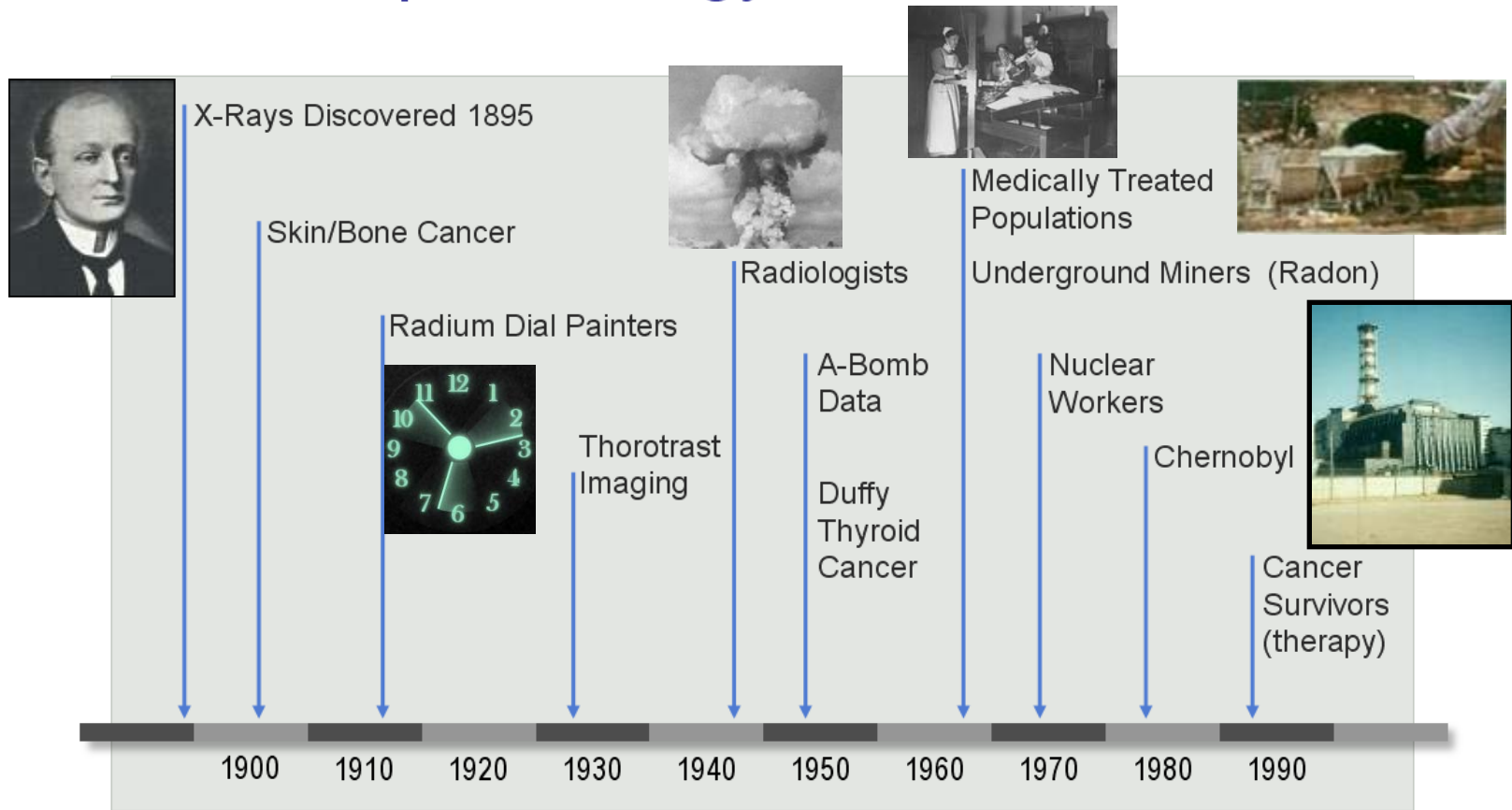


The New Yorker, Nov 26, 2001, Wm Hamilton

Wm Hamilton

Epidemiology is the study of the distribution and causes of disease in humans.

Radiation Epidemiology Dates Back 100 Years





Epidemiologic Studies of Exposed Human Populations



JAPANESE ATOMIC BOMB SURVIVORS

RADIOTHERAPY - CANCER

Cervical
Endometrial
Childhood
Breast
Hodgkin Lymphoma

RADIOTHERAPY - NON-MALIGNANT

Spondylitis
Thymus
Tonsils
Menstrual Disorders
Scalp Ringworm
Mastitis ←
Infertility ←
Otitis Media
Ulcer ←
Hemangioma

DIAGNOSTIC

TB - Fluoroscopy
Pelvimetry
Scoliosis
General

OCCUPATION

Ra Dial Painters
Miners (Radon)
Radiologists
Technologists
Nuclear Workers
Atomic Veterans

ENVIRONMENT

Chernobyl
Weapons Fallout
Natl Background
Techa River

RADIONUCLIDES

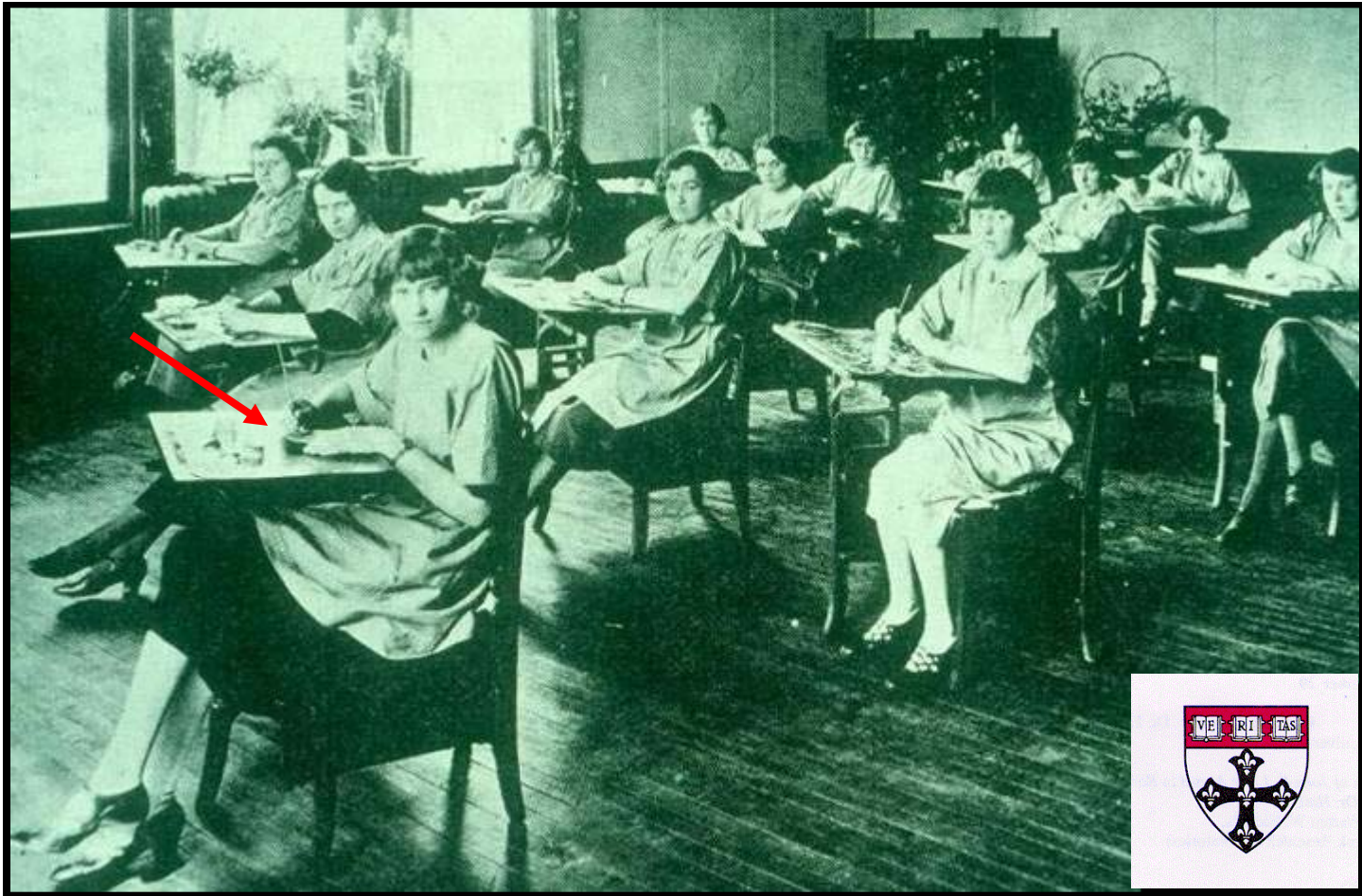
Thorotrast
I - 131
Uranium
P - 32
Ra - 224
Plutonium

Oldies but Goodies (Before 1950)

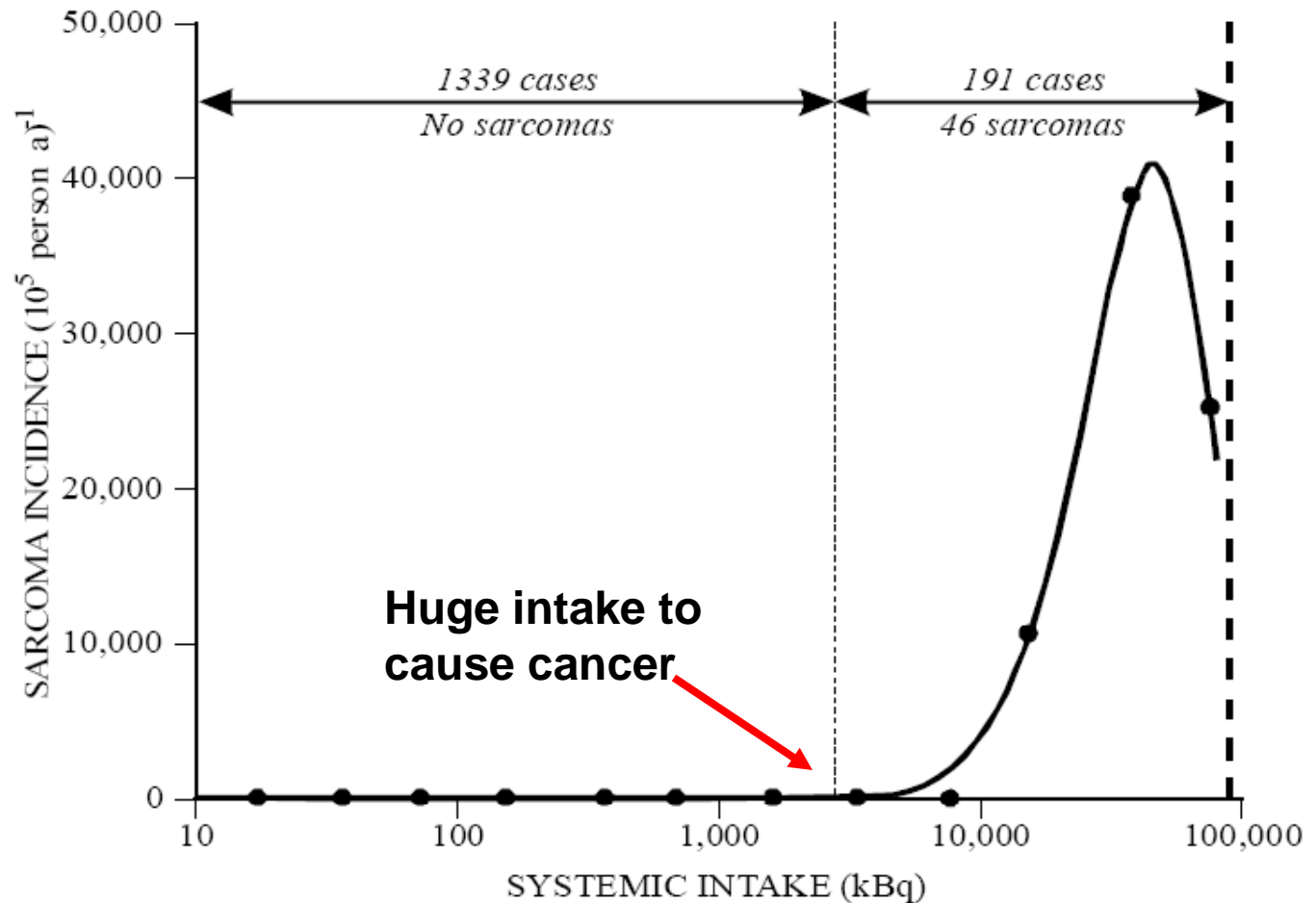
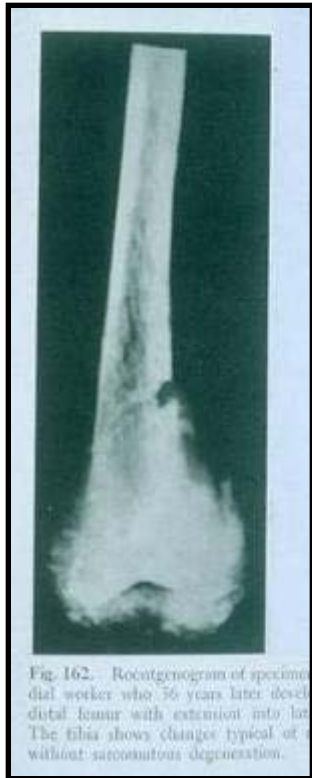
- Radium Dial Painters
- Thorotrast Patients
- Radiologists



Radium Dial Painters



Bone Cancer in Radium Dial Painters (UNSCEAR 2000; Rowland Rad Res 1978)



10 Gy suggested as a “practical threshold” for bone cancer

Bone Cancer, not leukemia

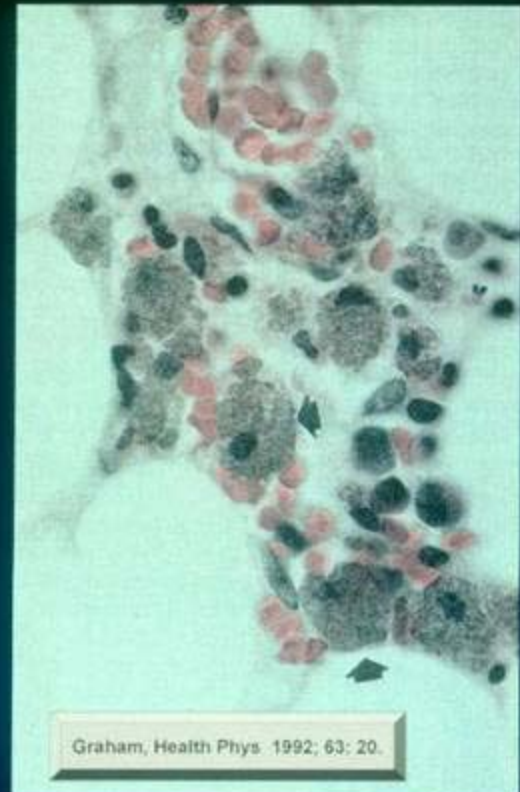
Thorotrast – Thorium Solution Contrast Agent



Abb. 1 Originalampulle "Thorotrast" (12 ml) der Firma Heyden. Daneben eine 25 ml Ampulle der Firma Fellows Testagar; dieses Präparat wurde nach 1947 nur für Tierversuche hergestellt.

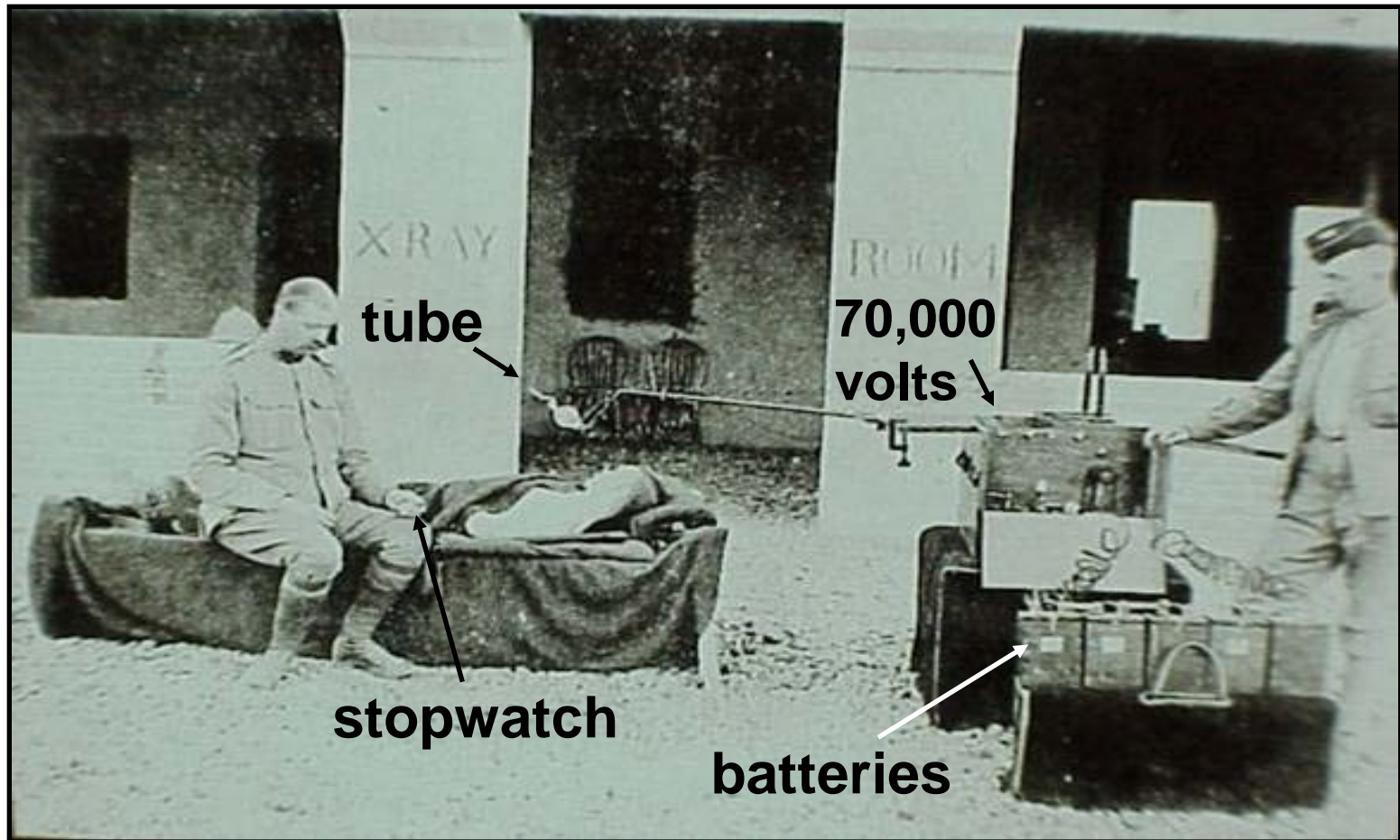
Photo, courtesy of Dr. Gerhard van Kalck.

Thorotrast in Bone Marrow

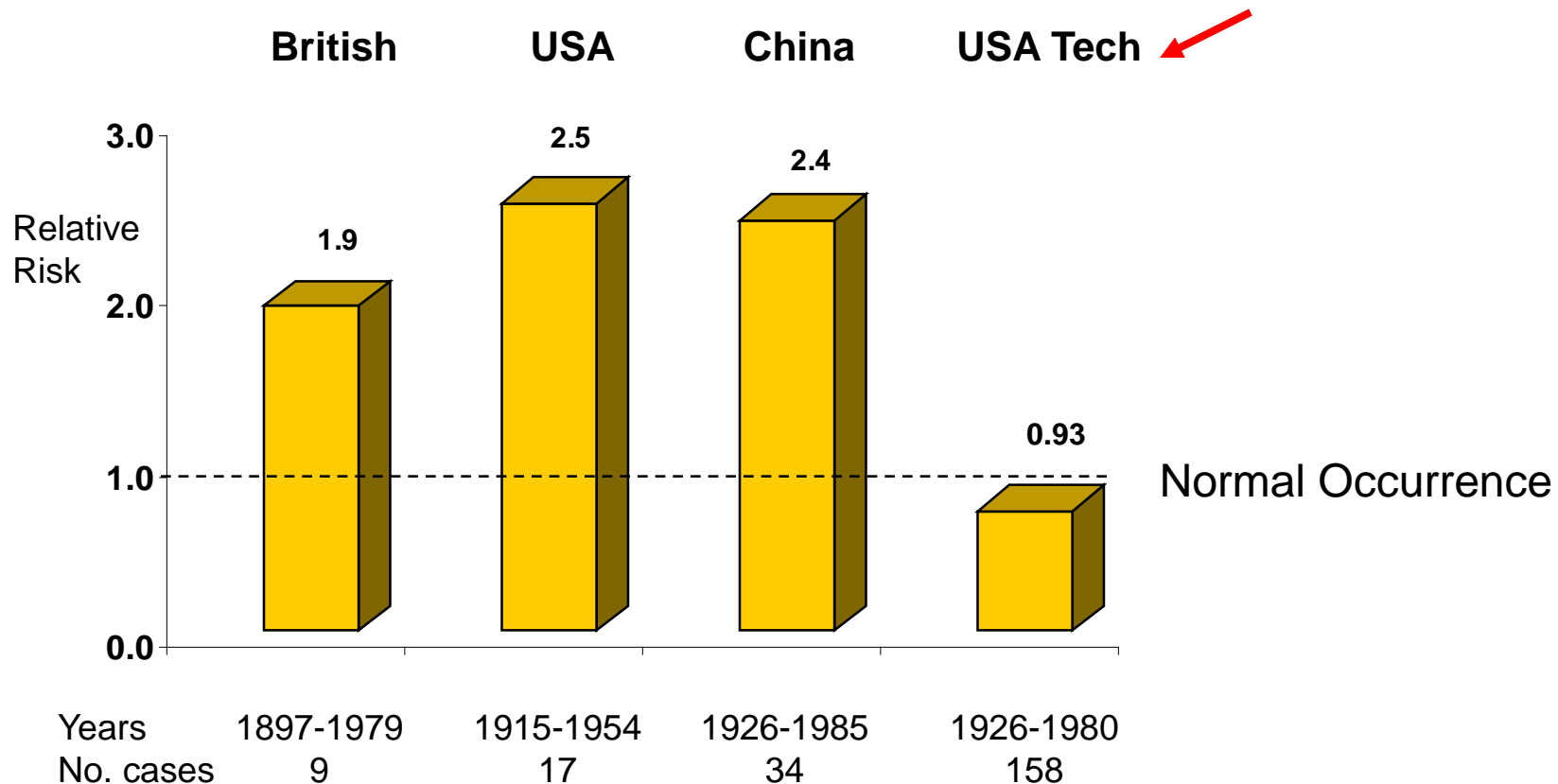


Graham, Health Phys 1992; 63: 20.

Early Radiologists and Technicians 1898 - Sudan



Leukemia Among Early Radiologists / Technologists



Berrington, *Br J Radiol* 74:507, 2001
Seltzer, *Am J Epidemiol* 81:2, 1965

Wang, *Int J Cancer* 45:889, 1990
Mohan, *Int J Cancer*, 2003

Early radiation workers

Radiation Exposure to Radiologists

1930: 100 rad / yr est.

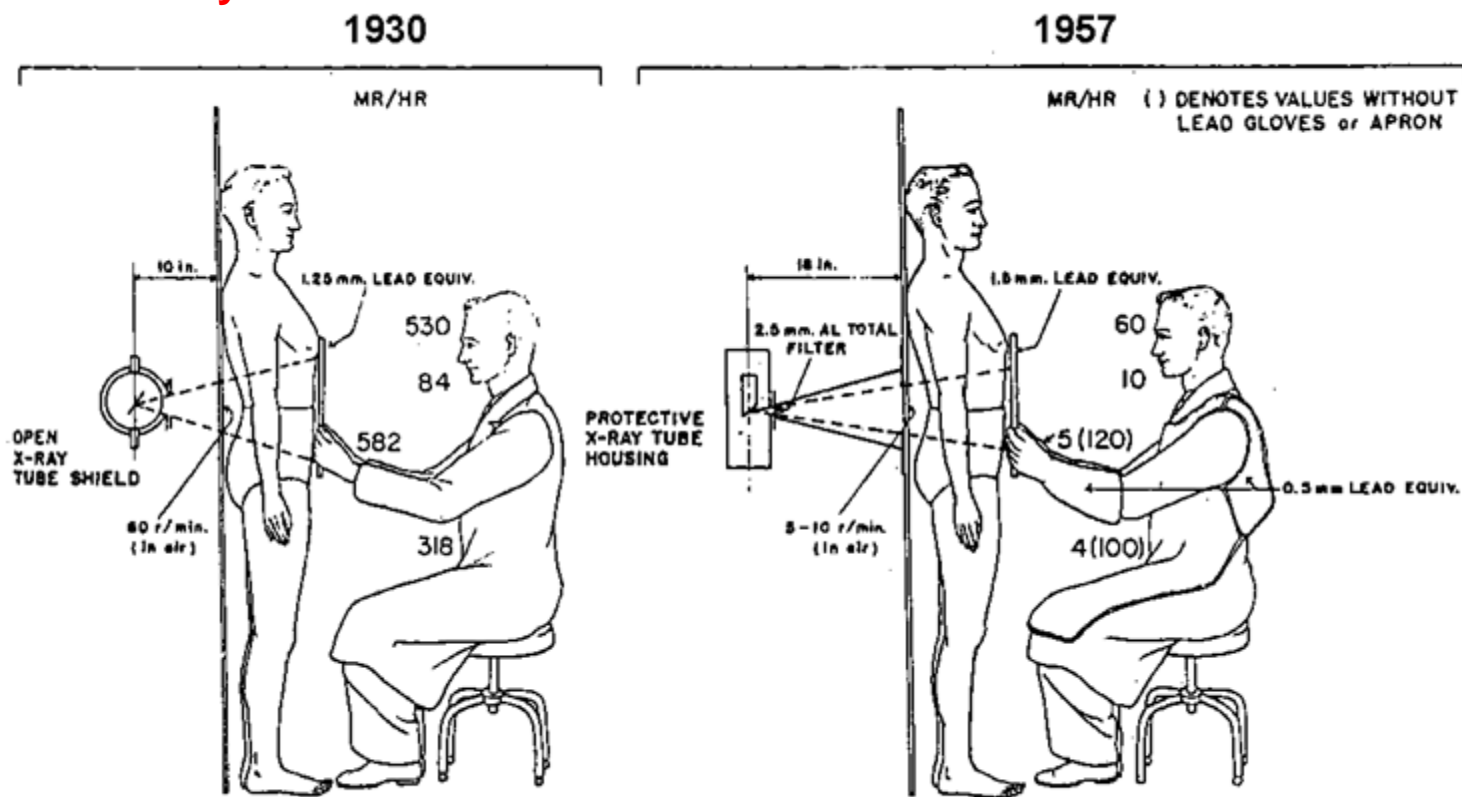


Fig 1. Comparison of stray radiation from vertical fluoroscopes.

Braestrup, *Am J Roentgenol* 78:988, 1957

Legendary Hits (1950-1970s)

- Ankylosing Spondylitis
- Cervical Cancer
- Prenatal X-ray
- Underground Miners



PRIVY COUNCIL

MEDICAL RESEARCH COUNCIL SPECIAL REPORT SERIES

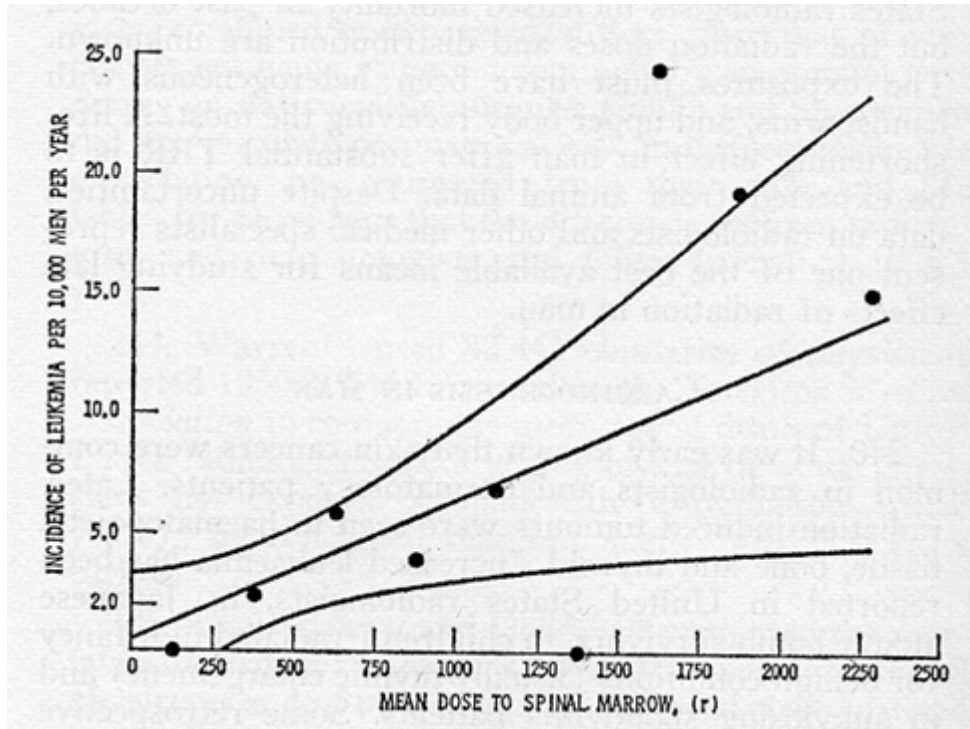
No. 295

**LEUKAEMIA
AND APLASTIC ANAEMIA
IN PATIENTS IRRADIATED
FOR ANKYLOSING SPONDYLITIS**

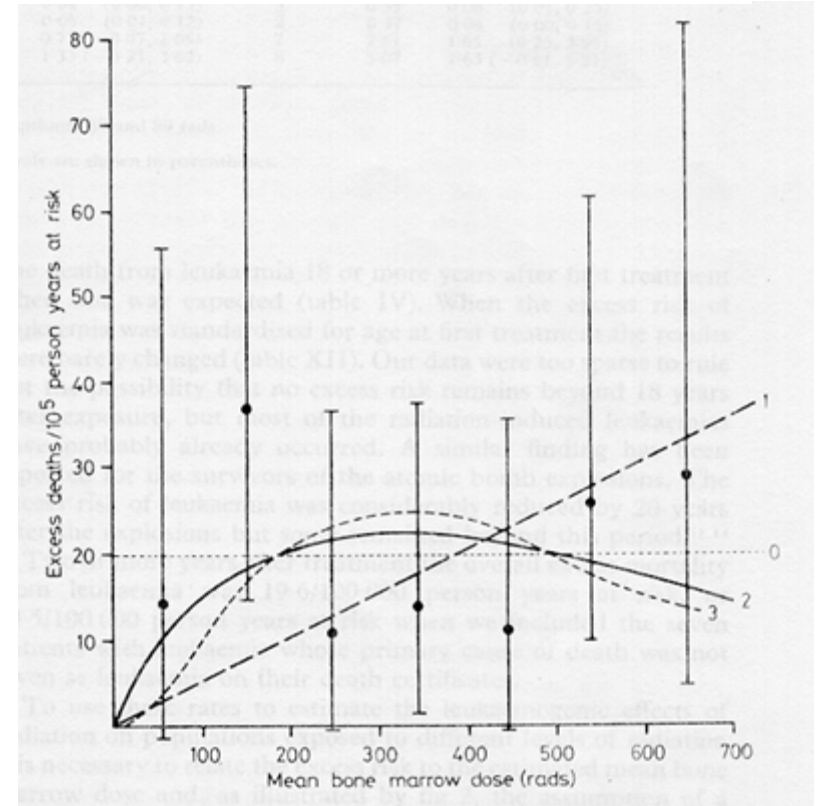
**W. M. COURT-BROWN, O.B.E., M.B., B.Sc., F.F.R.
and R. DOLL, O.B.E., M.D., F.R.C.P.**

1957

Leukemia - Ankylosing Spondylitis, UK



Court Brown & Doll, UK, 1957
UNSCEAR, 1962



Smith & Doll, *BMJ*, 284:449, 1982
Weiss et al, *Radiat Res* 142:1, 1995

Smith PG. [The 1957 MRC report on leukaemia and aplastic anaemia in patients irradiated for ankylosing spondylitis.](#) *J Radiol Prot.* 2007



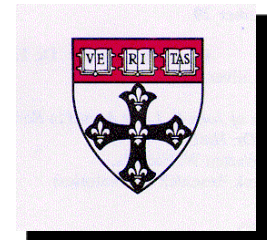
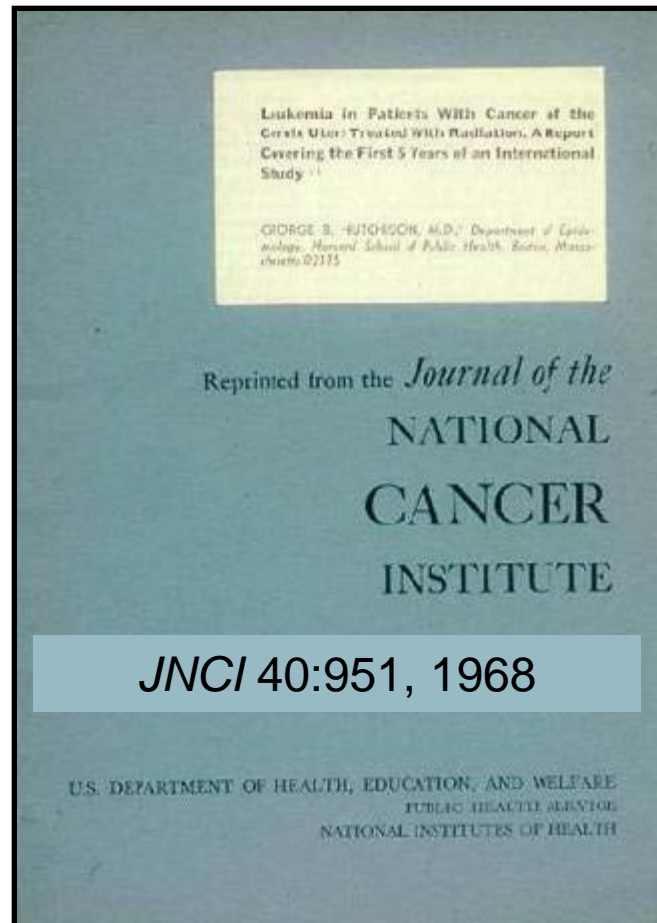
Sir Richard Doll on Ankylosing Spondylitis Study

“My favourite paper is the one with Michael Court-Brown deriving the dose–response relationship between radiation and leukaemia. . . . But this work is not often remembered nowadays. I doubt if many epidemiologists would pick the dose–response relationship between radiation and leukaemia if they were asked to associate particular observations with my work. Yet, it is certainly the second most important piece of work that I have done, after the effects of smoking, and it provided the first suggestive evidence of a linear relationship for the carcinogenic effect of ionising radiation down to quite small doses. In fact, the estimate of the risk of leukaemia per unit dose that it provided is not very different from the value that is accepted now.

“It was quite a difficult study to organise. We had to collect information on 14 000 patients treated throughout the country by radiotherapy for the benign condition of ankylosing spondylitis, and we had to measure the dose of radiation received in the marrow by doing experiments on a model man. In many ways it was the best-designed study I have ever participated in and possibly my best work.”

Study of Leukemia Radiotherapy for Cervical Cancer

Third study in
1960s designed
to quantify risk of
leukemia



Cervical Cancer and Leukemia

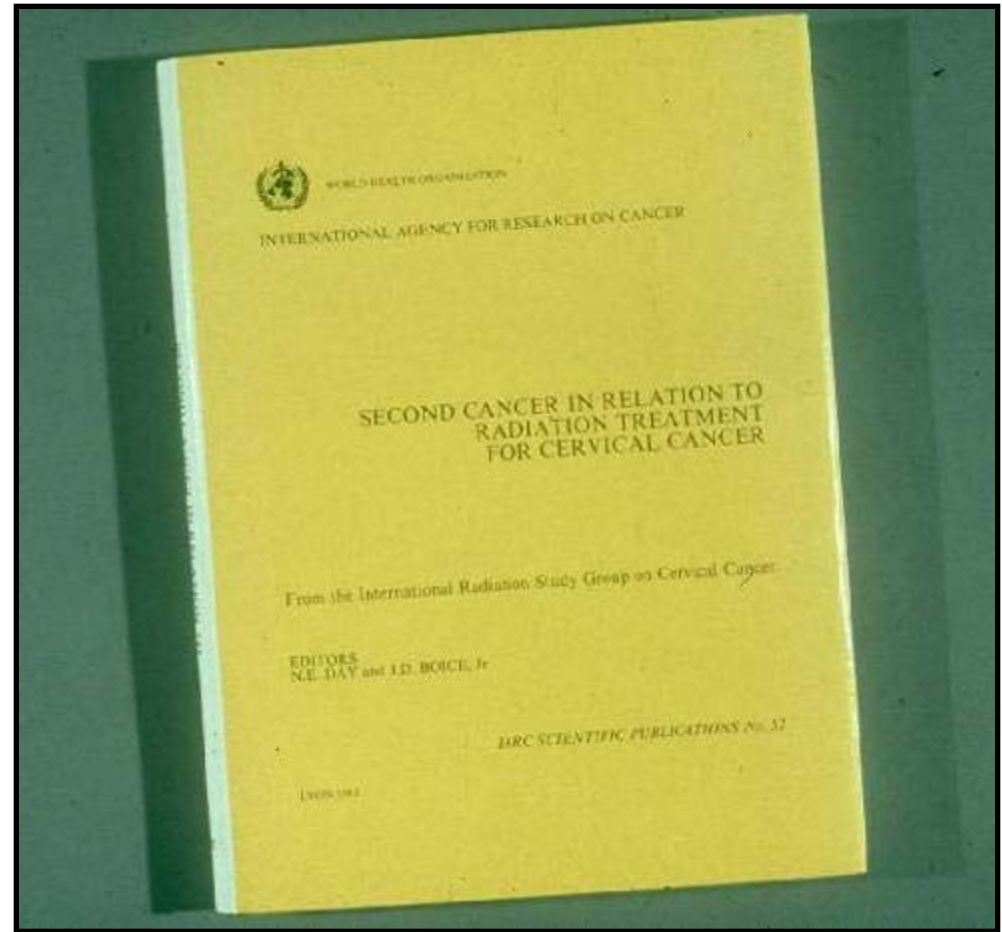
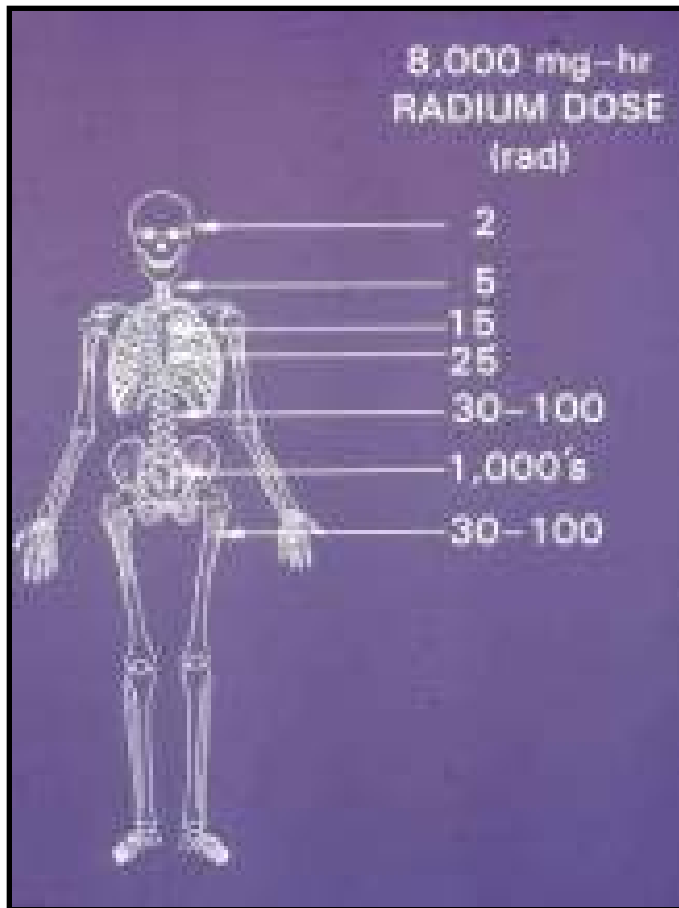
Blood Studies and Clinical Follow-up

30 Radiotherapy Centers in 9 Countries



Number	30,000 women
Dose	5-15 Gy (marrow)
Leukemia	
Observed	13
Expected	15.5
Risk	No excess

International Cervical Cancer Study Expansion – 16 Radiotherapy Centers and 17 Cancer Registries in 14 Countries



200,000
women



LEUKEMIA

Radiotherapy for Cervical Cancer

LEUKEMIA TYPE	RAD	NUMBERS		RR	(90% CI)
		CASES	CONTROLS		
AL + CML	YES	133	489	2.0	(1.0-4.2)
	NO	8	56		
CLL	YES	48	183	1.0	(0.3-3.9)
	NO	4	16		

AL-ACUTE; CML-CHRONIC MYELOID; CLL-CHRONIC LYMPHOCYTIC LEUKEMIA
BOICE et al, JNCI 79:1295, 1987

Elis Berven (1885-1966) på Radiumhemmet

Radiumjournal för *Fru*
 Nr *442* år 191*8* Ad
 Diagnos *Ca. Cervicis uteri.* Beh.-res.

Behandlingslokal	1918	Dat.	Apparat	Dos	Tid	Filter- mm.	Sek. filter
i cervixkanalen	21/8	1 Tub	70	20		1 mm	
i vagina (3+2, 4+1)	"	8 Tubu	160	20		3 mm	
i cervixkanalen	28/8	1 Tub	60	20			
i vagina	11/8	10 Tubu	100	20			
i uterinkavitet	2/9	8 an	95	20			
i vagina	"	13 Tubu	140				

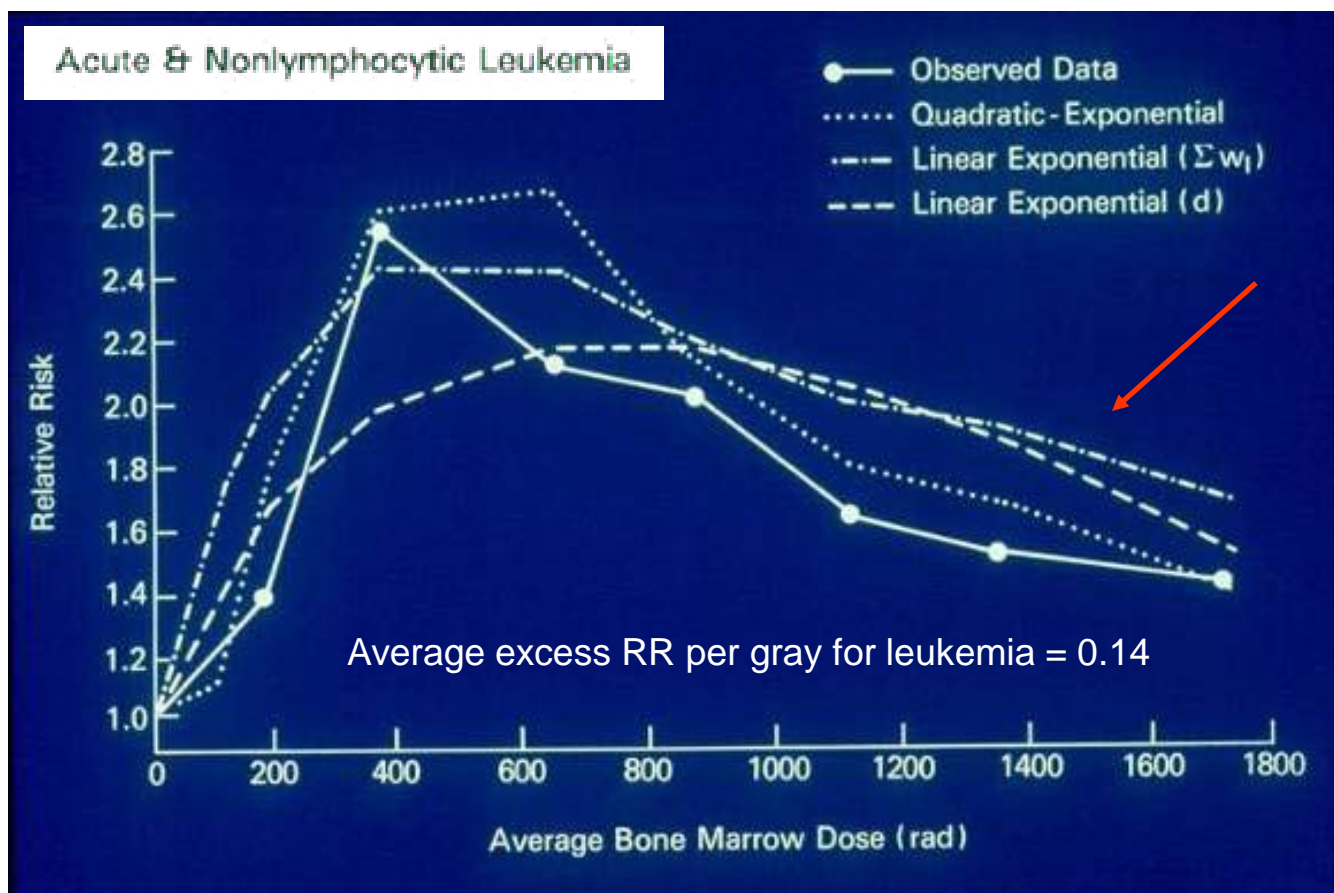
H. B. SÖDERBERG, Förf. Skrift. GÖTEB.

Radiumjournal

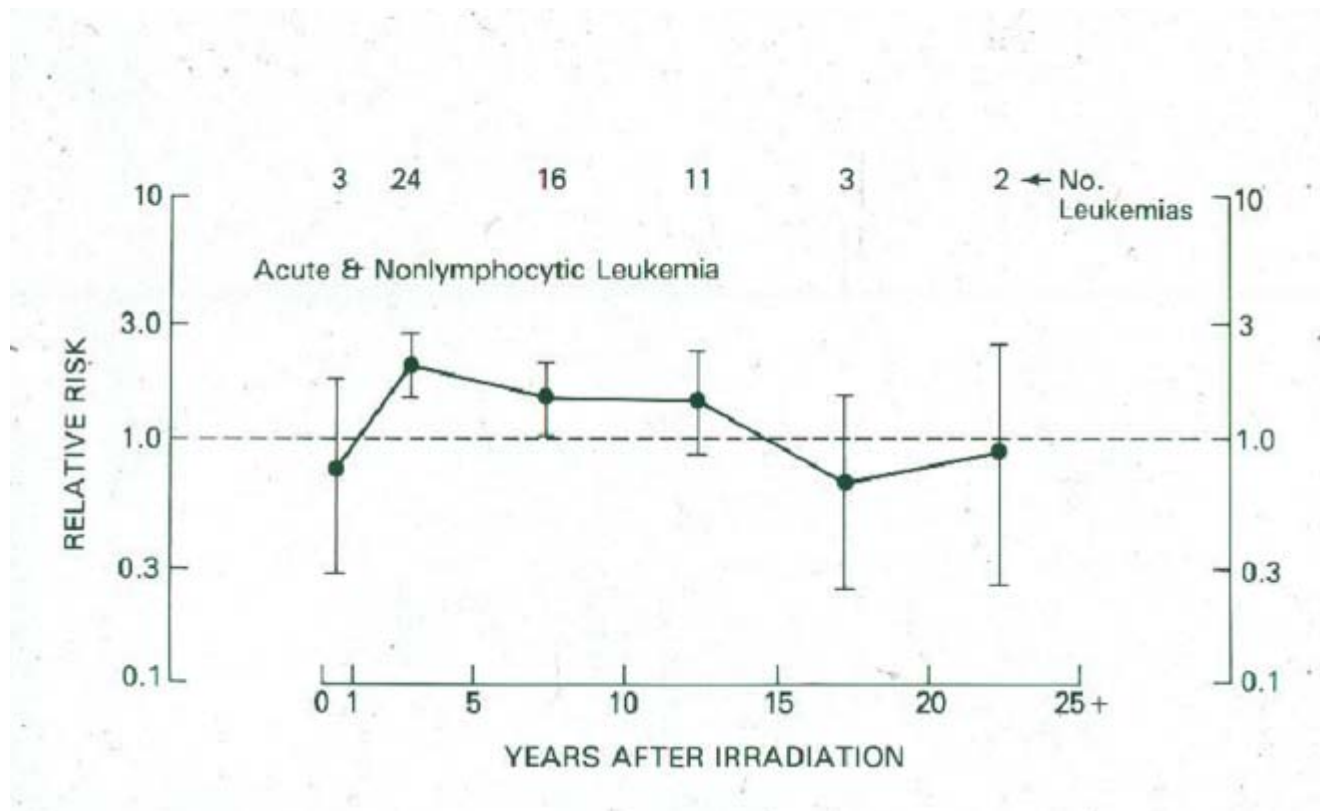
År 1918



Bone Marrow Dosimetry Downturn at High Doses

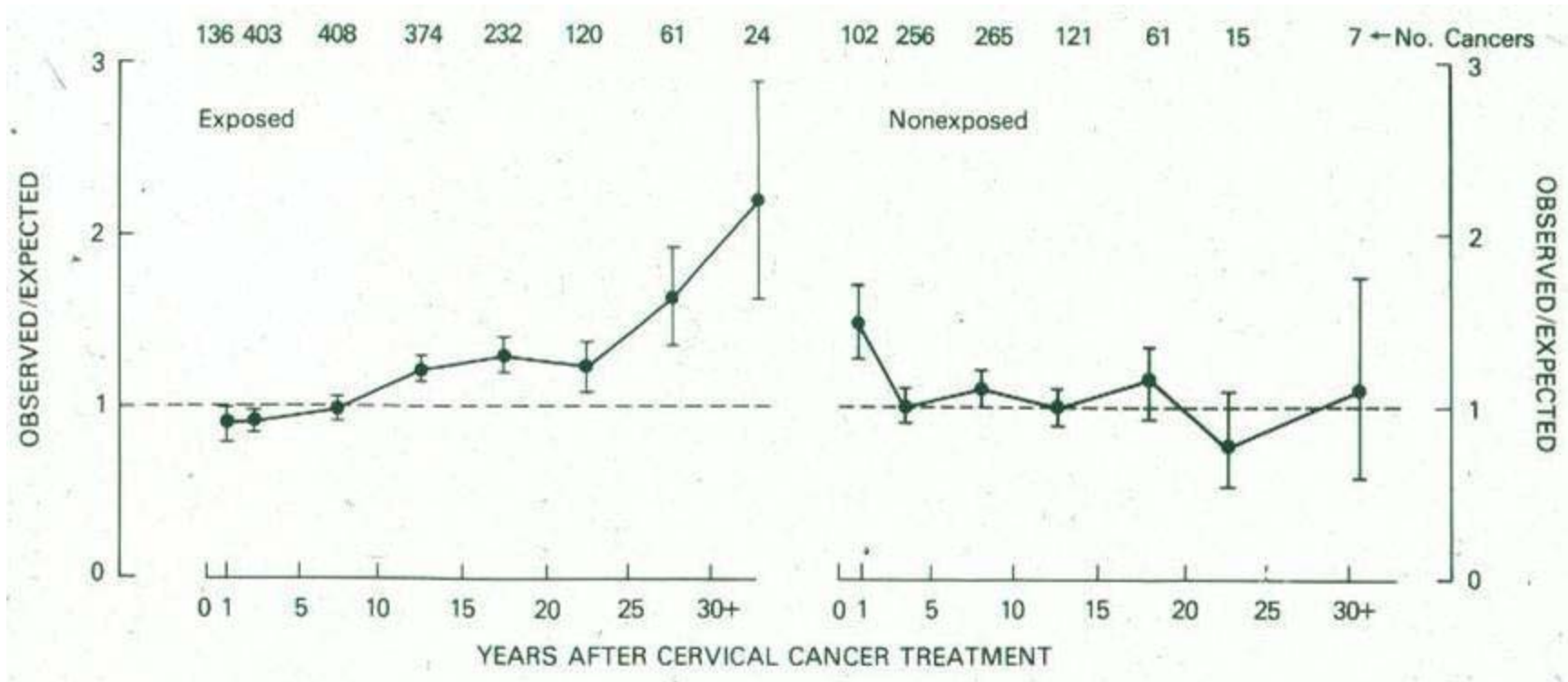


Characteristic Wave-like Pattern for Radiation-Induced Leukemia



Boice, *JNCI*, 74:955, 1985

Solid Cancers After Radiotherapy Long Minimum Latency





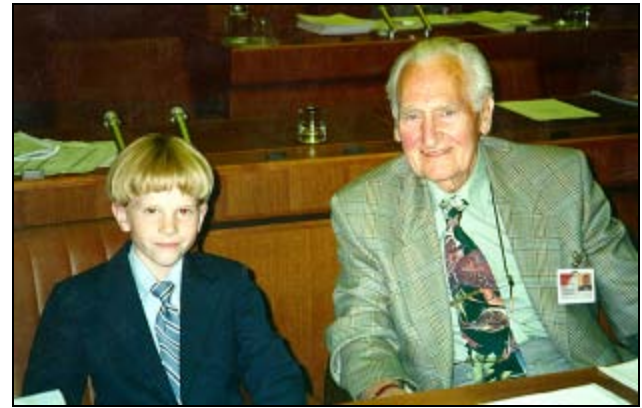
Oxford Prenatal X-ray Survey

Is the low-dose association causal?



Childhood cancer	Cases	% X-ray	RR
Leukemia			
Lymphatic	2,007	14	1.5
Myeloid	866	14	1.5
Lymphoma	719	13	1.4
All leukemia/lymphoma	4,771	14	1.47
Wilms	590	15	1.6
CNS	1,332	13	1.4
Neuroblastoma	720	14	1.5
Bone	244	11	1.1
Other solid	856	15	1.6
All solid	3,742	14	1.47

WM Court Brown, R Doll, A Bradford Hill – No Cohort Study is Positive



“Altogether information was obtained about 39,166 liveborn children whose mothers were known to have been subjected to abdominal or pelvic irradiation during their pregnancy. Among their children, nine were discovered to have died of leukaemia before the end of 1958. The expected number was estimated to be 10.5...

It is concluded that an increase of leukaemia among children due to radiographic examination of their mother's abdomen during the relevant pregnancy is not established.”

BMJ November 26, 1960



ICRP Publication 90 (2003) Biological Effects after Prenatal Irradiation (Embryo and Fetus)

“ Although the arguments fall short of being definitive because of the combination of biological and statistical uncertainties involved, they raise a serious question of whether the great consistency in elevated RRs, including embryonal tumours and lymphomas, **may be due to biases** in the OSCC study rather than a causal association. ”

Christian Streffer, Chairman

RADON AND LUNG CANCER RISK

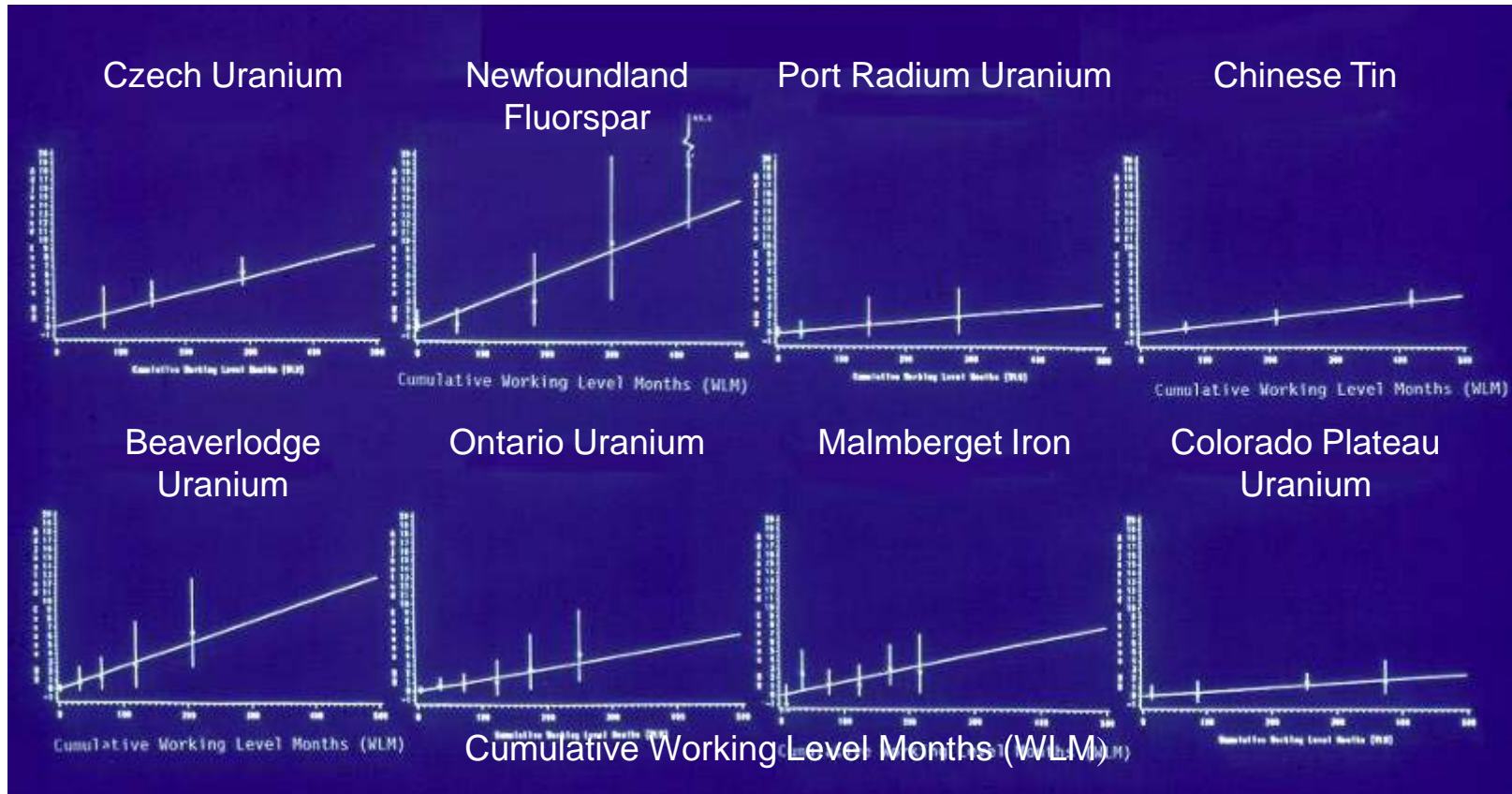
RADON AND LUNG CANCER RISK:

**A JOINT ANALYSIS OF
11 UNDERGROUND MINERS STUDIES**



NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Lung Cancer Dose Responses in Miners Consistency in the Epidemiology



The Study Team - 1992



Radon Interacts with Smoking to Enhance Risk

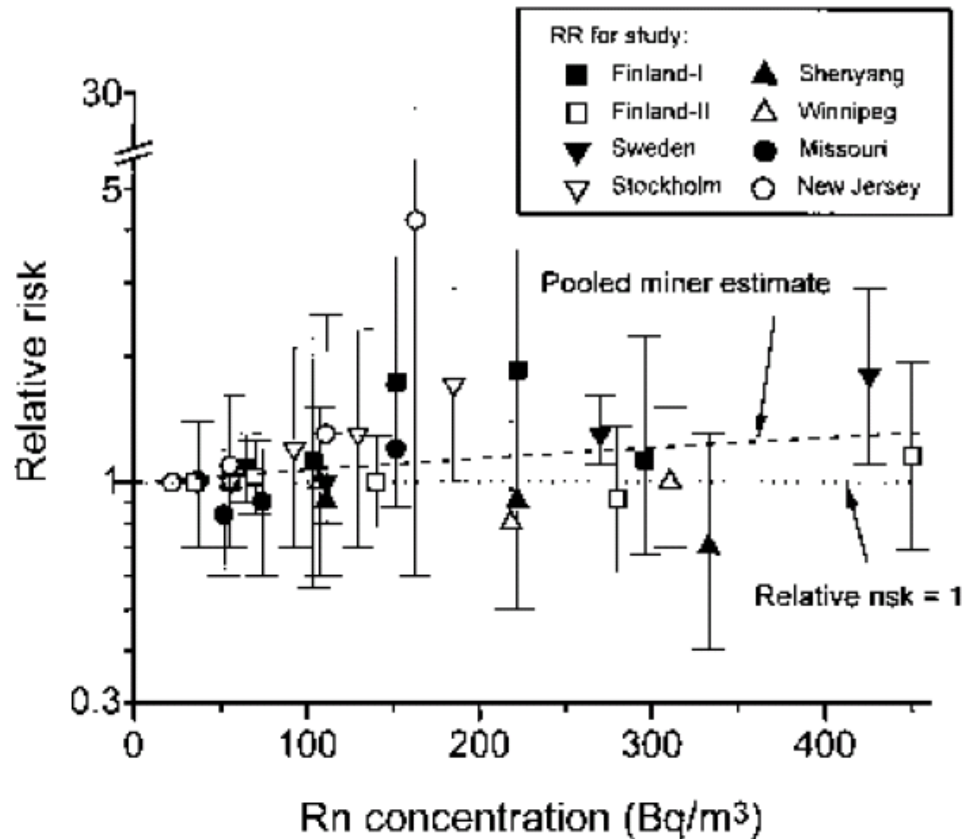


A nearly
multiplicative
interaction

NRC, BEIR, 1999



Indoor Radon Meta-Analysis 4,263 Lung Cancers



Difficult to detect low-dose risks, yet significant trend when studies combined

Gold and Platinum Honors (1950+)

- Japanese Atomic Bomb Survivors
- Pooling – Thyroid
- Pooling – Breast



Pregnancy and A-Bomb Radiation

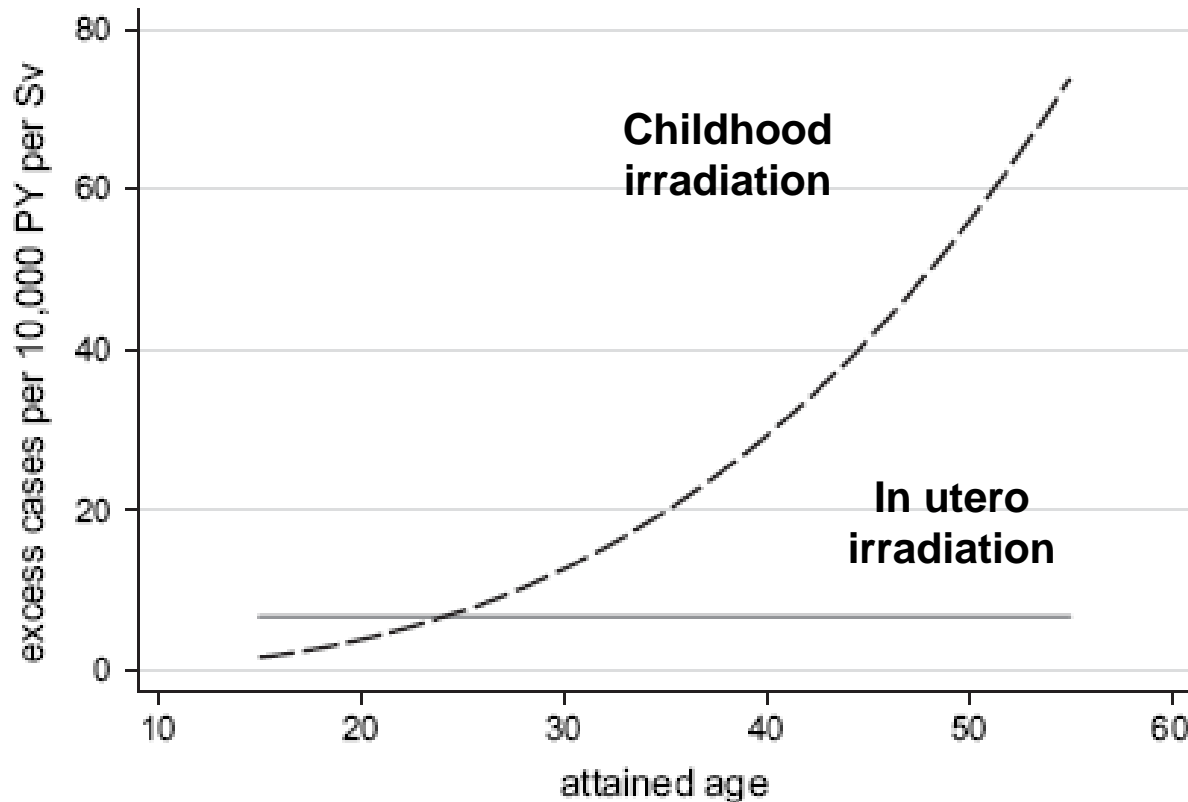




Atomic Bomb Survivors In Utero and Post-Natal Cancer Risk



Risk of
Cancer



No apparent
increased
sensitivity

No childhood
leukemia

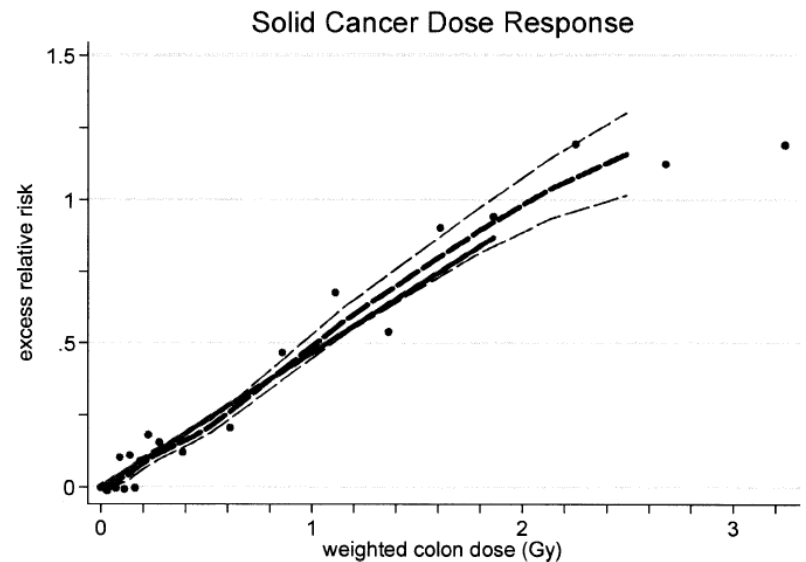


Epidemiologic Studies are the Basis for Cancer Risk Estimates.

“ Radiation risk estimates are derived for incidence data for specific tumour sites when adequate dose response data are available from the **Japanese Life Span Study (LSS), pooled analyses of multiple studies, or other sources.**” ICRP Publ 103, 2007



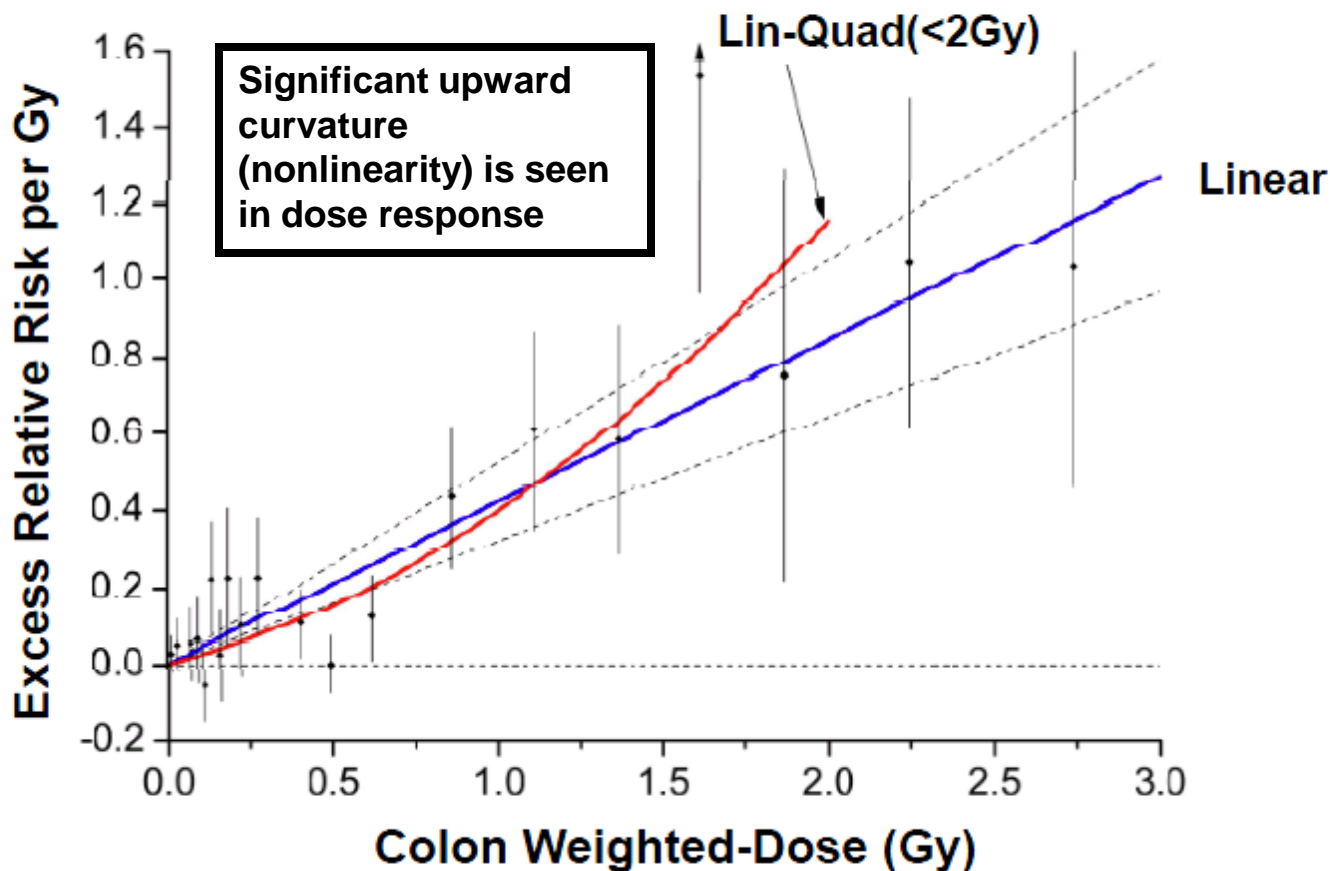
1945, Japan, war torn, acute exposure



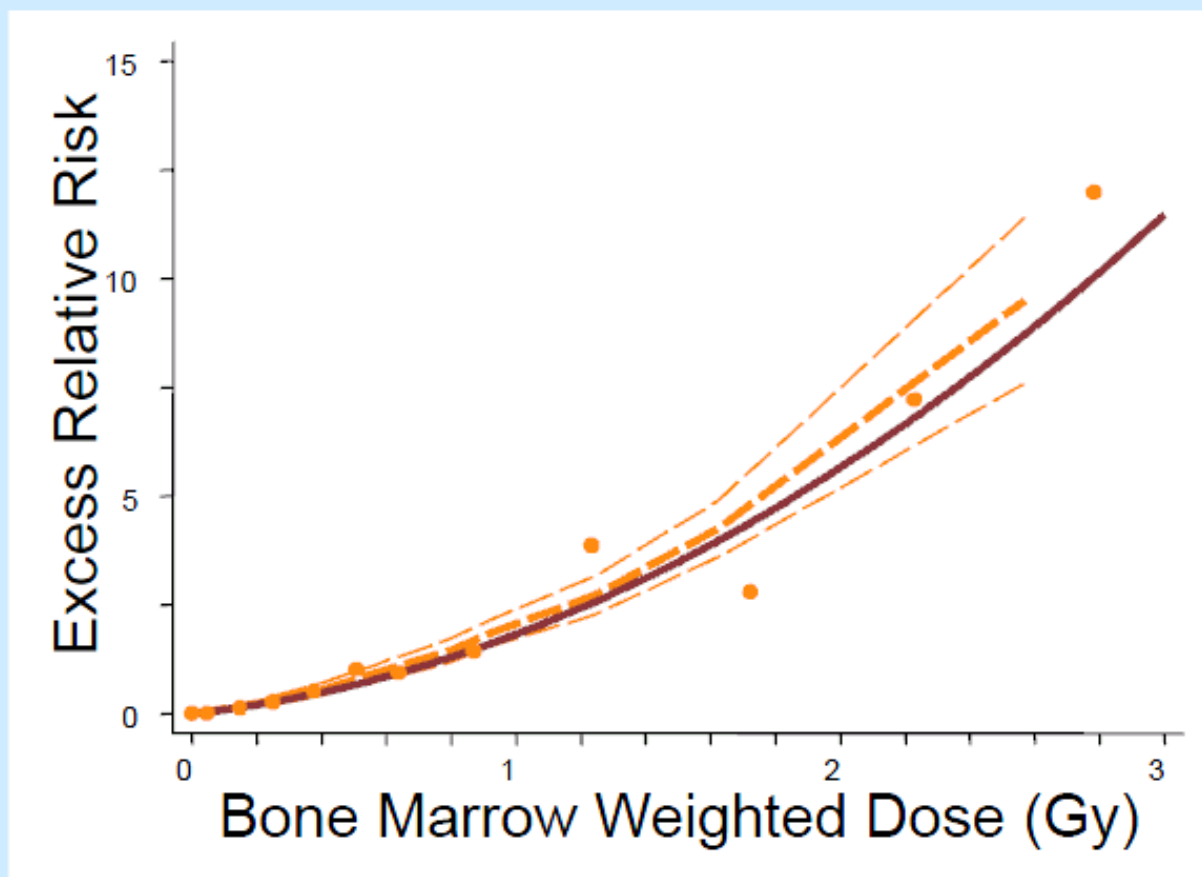
Preston, *Rad Res* 168:1, 2007

Cancer Incidence, 1958-1998

LSS Dose-Response for Solid Cancer Mortality, 1950-2003



LSS Leukemia Dose Response



Linear-quadratic fits better than Linear model.

Dose-threshold estimate: 80 mGy (95% CI: 30, 190 mGy)

(Hsu et al, Unpublished, 2010)

Pooled Analyses



Art Schneider, E Ron Symposium 2011

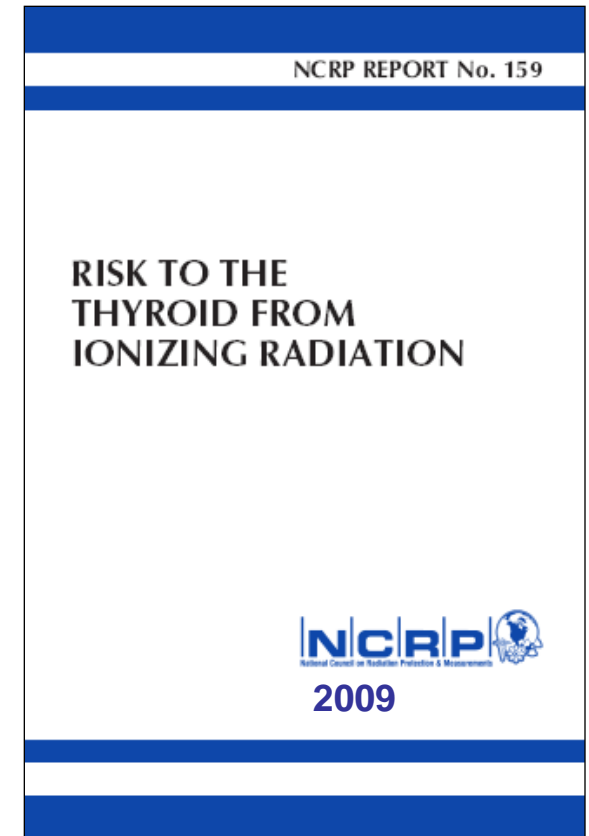
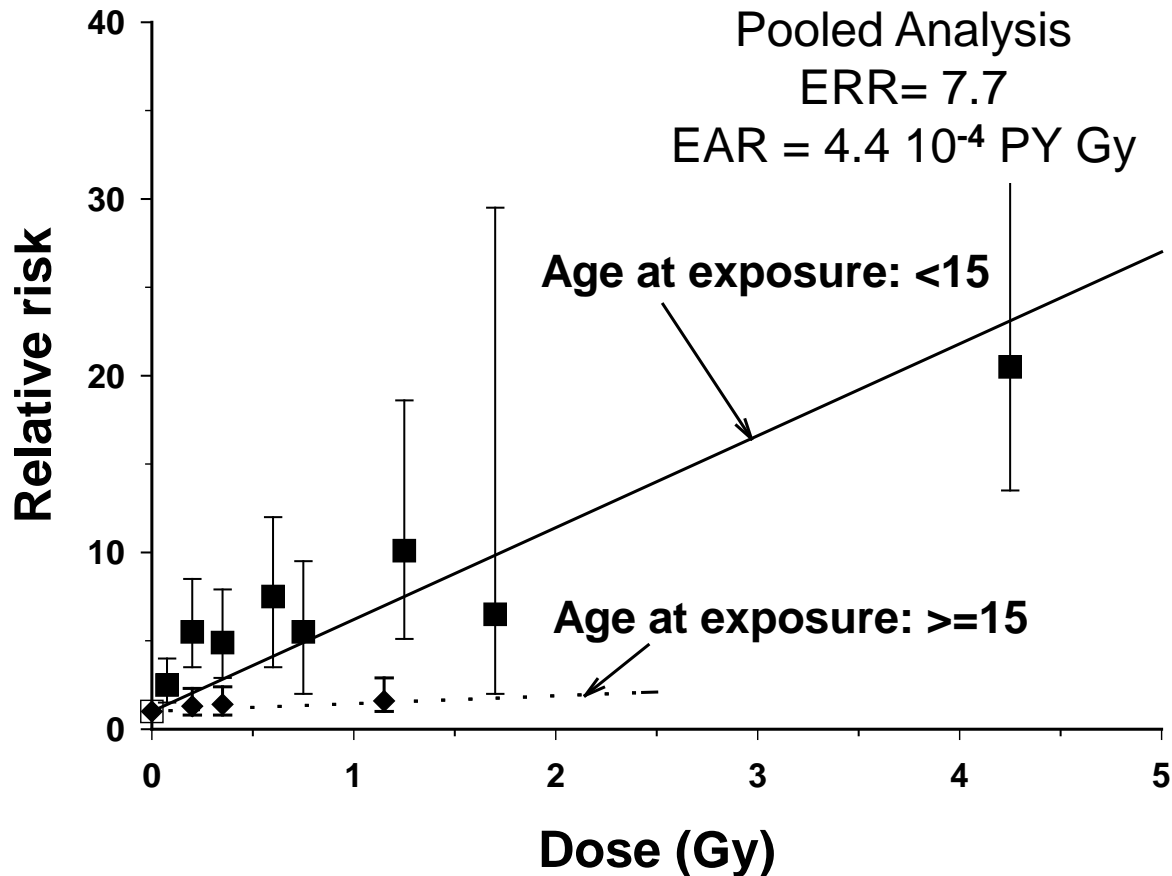
Thyroid Cancer after Exposure to External Radiation: A Pooled Analysis of Seven Studies



Ron et al, 1995

Thyroid Cancer & External Radiation Risk

Dose Response by **Age** at Exposure



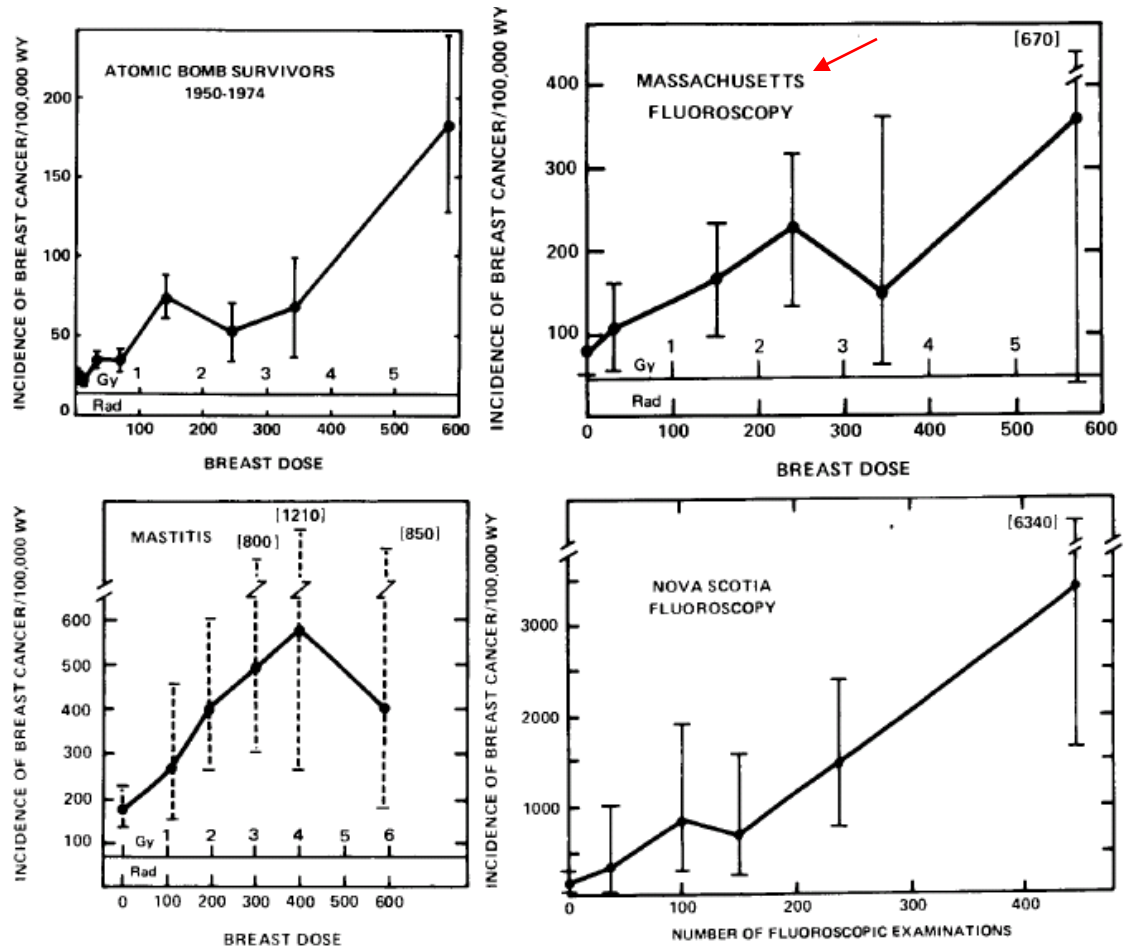
Radiation Effects on Breast Cancer Risk: A Pooled Analysis of Eight Cohorts



Dose Response – Pooled Analysis of Breast Cancer Studies

Breast Cancer

Consistent with linearity



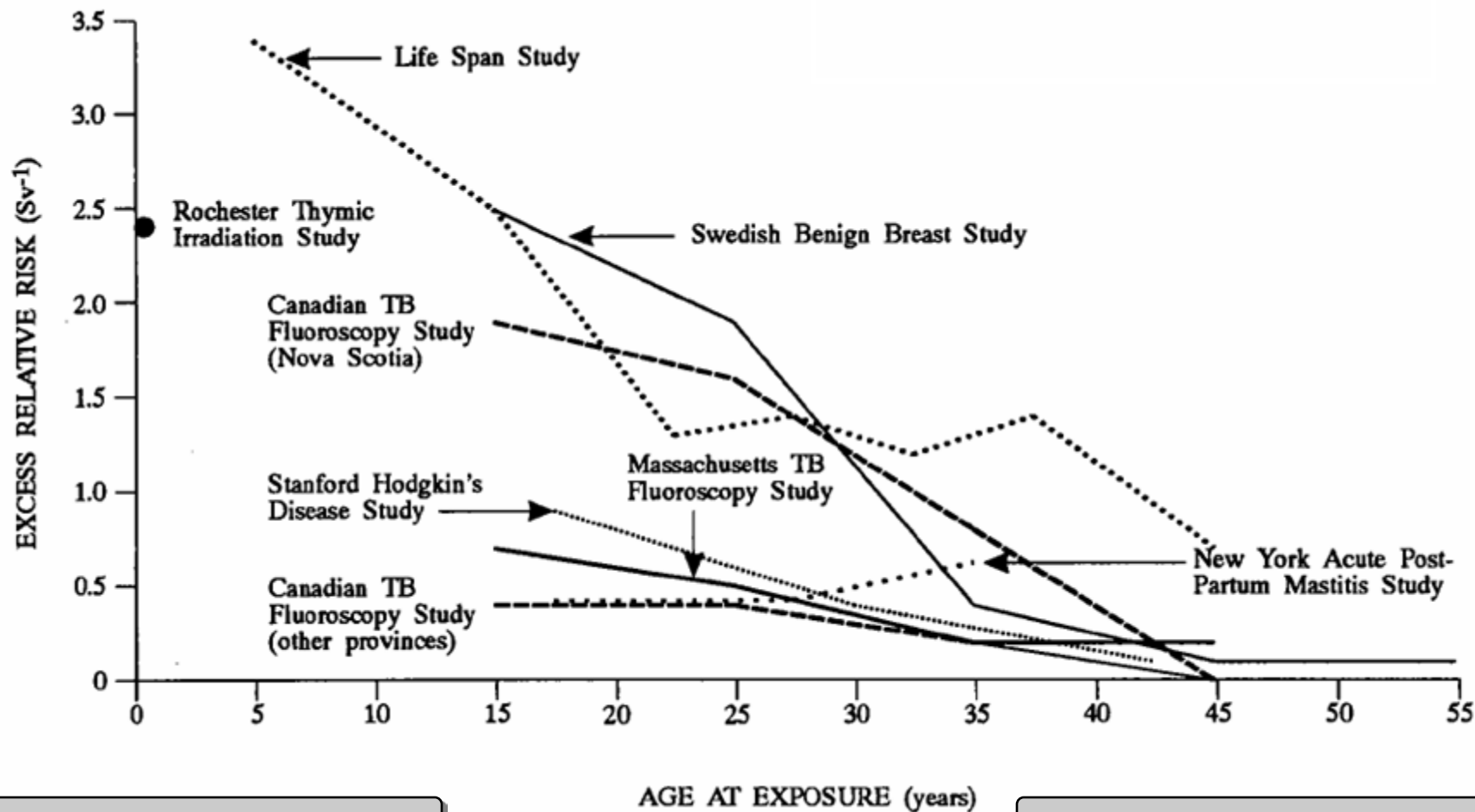
Boice, *Radiology* 131:589, 1979

Land et al. *JNCI* 1980

Preston et al. *Rad Res* 2002

Age at Exposure

Radiation-Induced Breast Cancer Studies



UNSCEAR, p. 155, 1994

Preston et al. *Rad Res* 2002

Hall of Fame (1950-1970s)

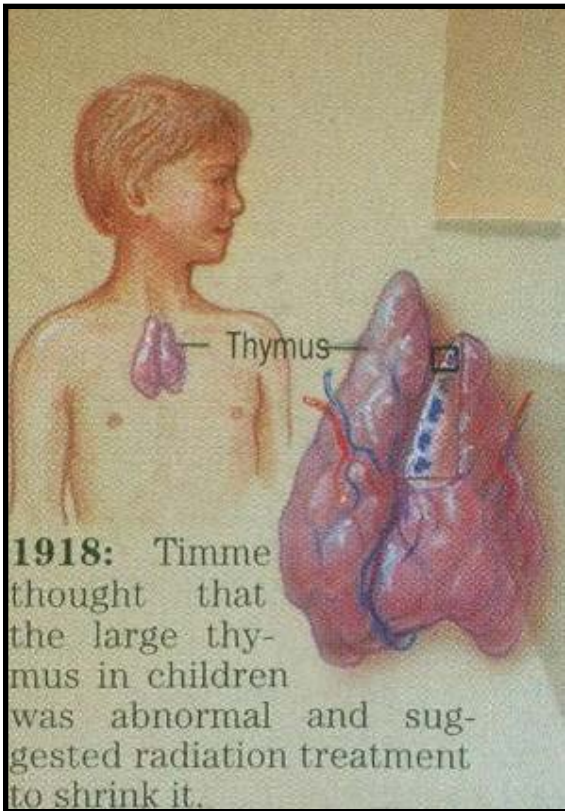
- Thymus
- Tinea Capitis
- Hemangioma
- I-131
- Tuberculosis





Thyroid Cancer Thymus Irradiation

In 1950 Robert W Miller MD was assigned by Atomic Energy Commission to University of Rochester. In his Memoriam to [Hempelmann](#) (1993) he wrote:



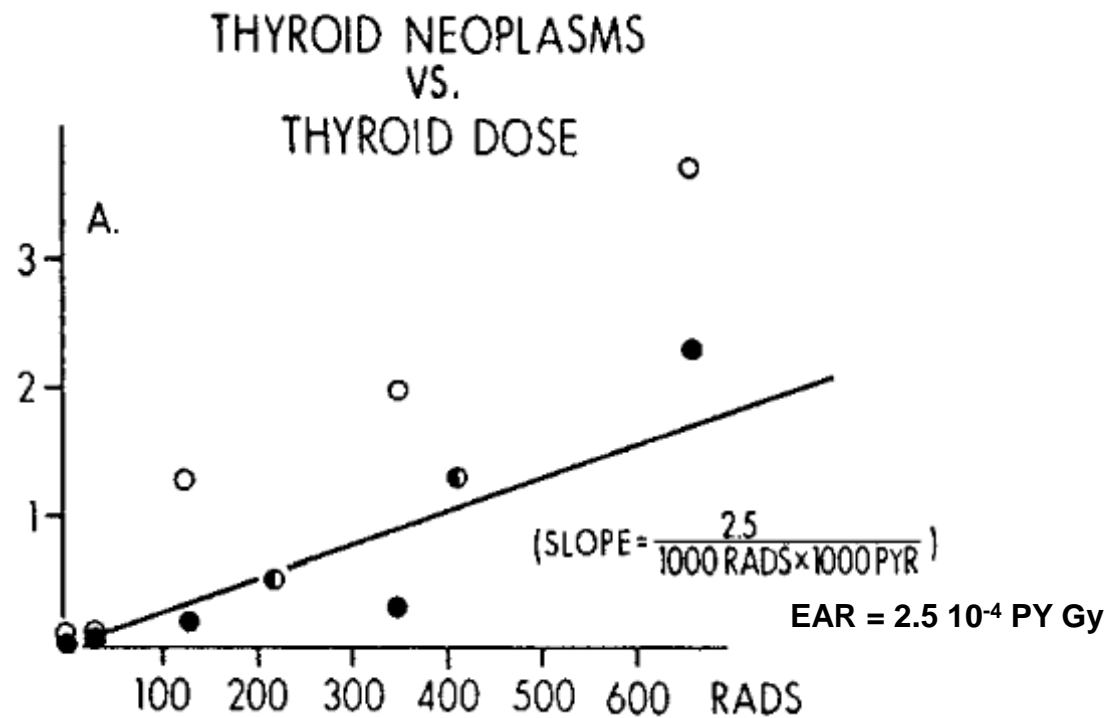
“In 1950 he [[Hempelmann](#)] joined the faculty at the University of Rochester as an Associate Professor of Experimental Radiology. [Benedict Duffy](#), who came to a neighboring department soon after, had just published on a case-series of 28 children who had developed thyroid cancer. Surprisingly, 10 had received thymic radiotherapy as infants.

At the same time, *a pediatrician from the Atomic Energy Project* at the University noted that when x-ray films were ordered on small children, fluoroscopy (high dose) was done routinely, as required by the Radiology Department. The Chairman of Radiology believed that fluoroscopy provided better information on a squirming youngster. Pediatricians began to write on the x-ray requests, "Film only, no fluoroscopy." *An unfriendly interdepartmental meeting led to a change in policy after it was shown that a 3-pound infant had received seven fluoroscopies plus 75 R to the thymus in the first month of life. Soon after, Louis [Hempelmann], who was at the meeting, began his now-famous studies of infants who had been given radiotherapy for thymic enlargement.*

Incidence of Thyroid Neoplasm (Hemplelmann et al. *Science* 1968; JNCI 1975)

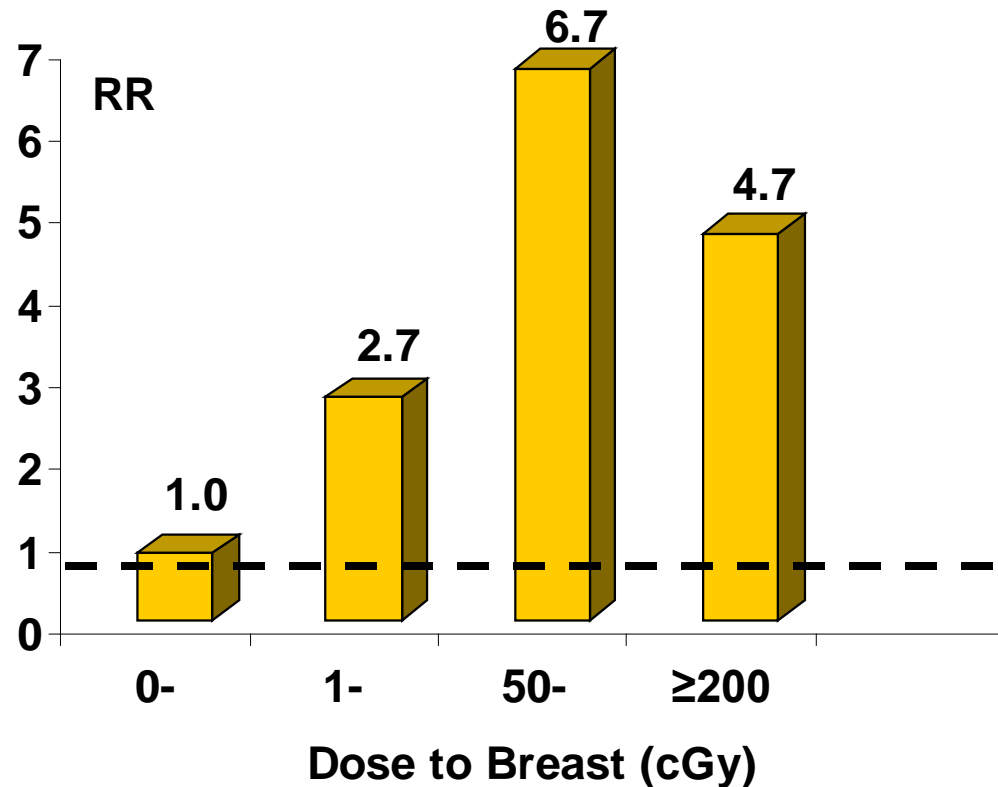
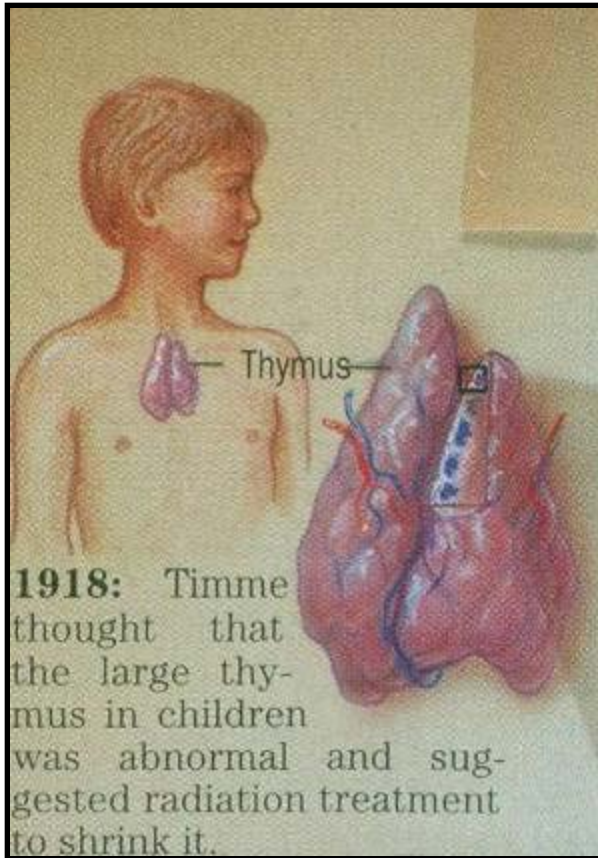


Louis Hempelmann with
J Robert Oppenheimer



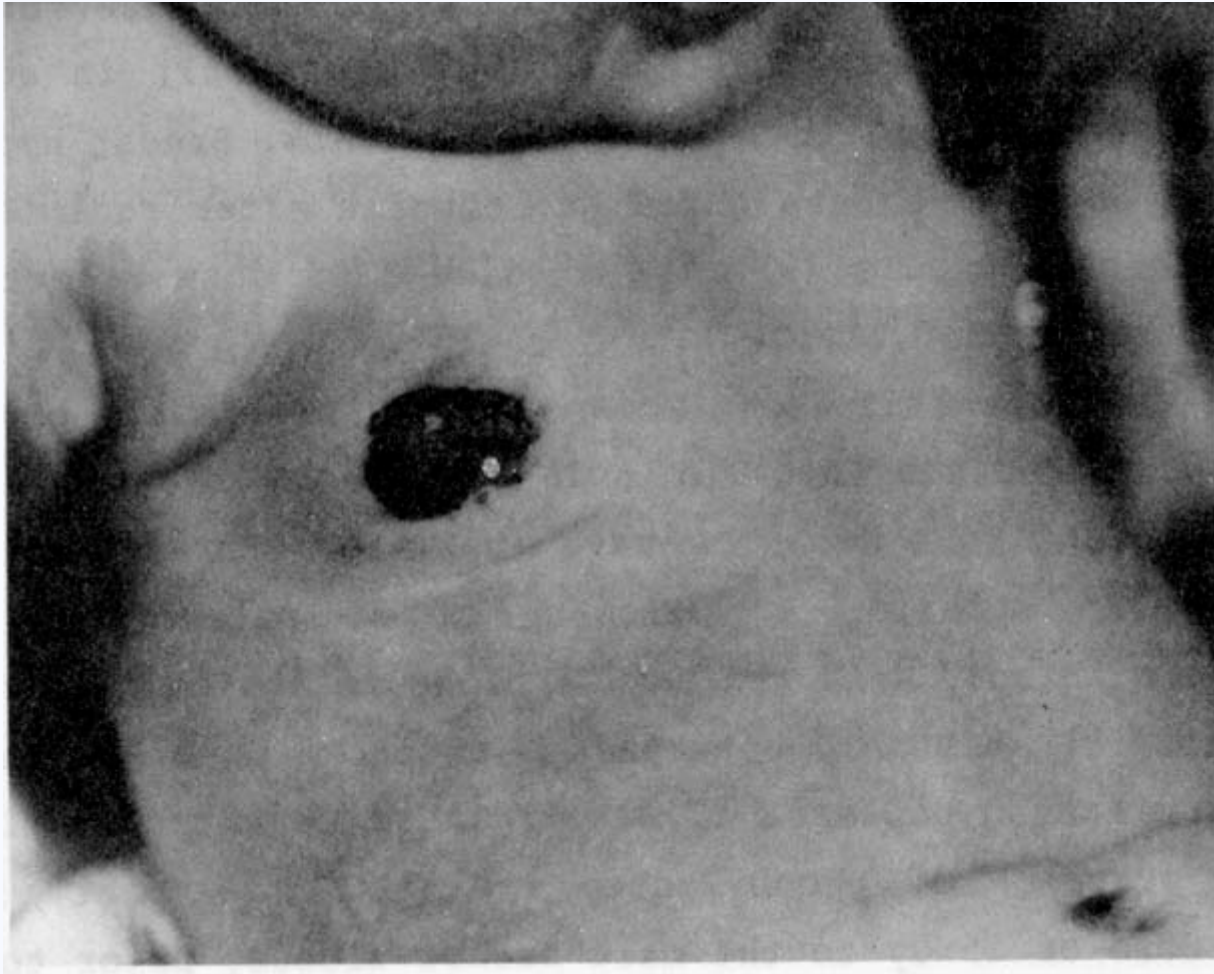
Update: Adams et. al. *Rad Res* 2010

Breast Cancer Thymus Irradiation



Hildreth et al, *NEJM* 321:1281, 1989

Immature breast tissue at risk but risk manifests many years later.



**Cavernous Hemangioma in girl, 6 months old
1936, Ra-226, 6.6 Gy to breast**

Breast Cancer After Infant Exposure

Dose Rate Reduction (DDREF = 7)

Study Exposure	Breast Dose (Gy)*	Number Treated	Breast Ca	Excess Risk (10 ⁴ WY- Gy)
Thymus				
High-dose-rate X-rays	0.7	3,312	34	34.0
Hemangioma				
Low-dose-rate Gamma radiation	0.4	17,082	226	5.1

*Ranges (0.02-7.5 Gy) & (0.02-35 Gy)

Preston et al, *Radiat Res*, 158:220, 2002

Consistent with a *low dose rate* having a smaller effect



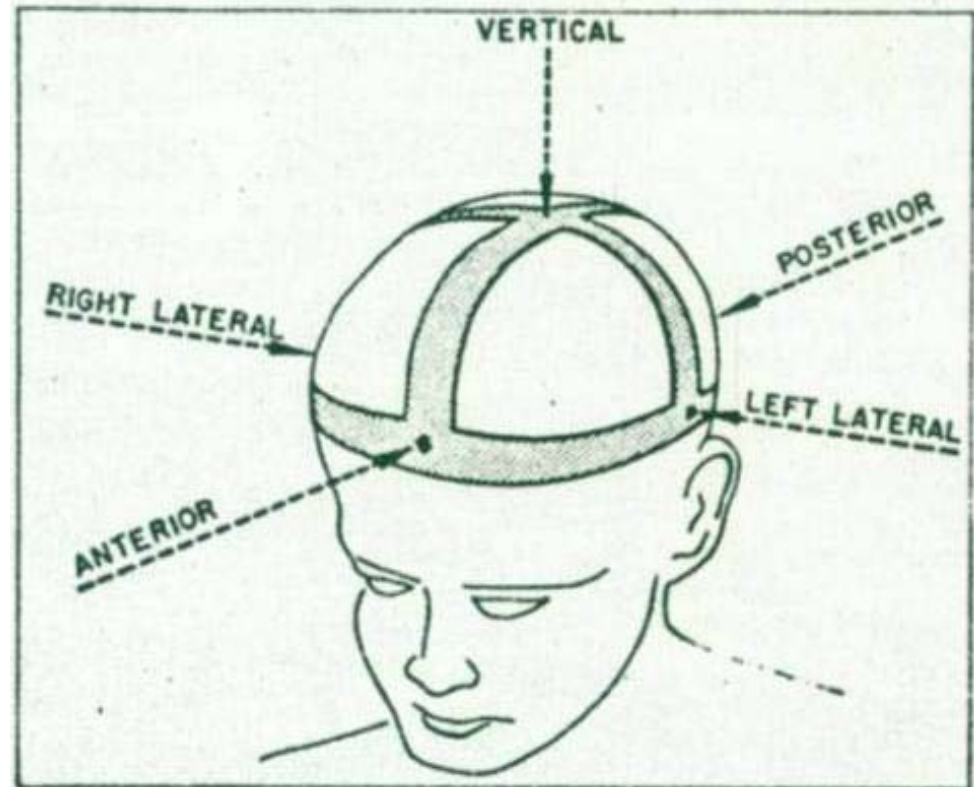
Radiotherapy for Ringworm

5 treatments, 3-12 minutes each



TINEA CAPITIS WITH KERION FORMATION
11-YEAR-OLD BOY WITH 3 YEAR INFECTION

Fig 1.—Five Treatment fields used in the Adamson-Kienbock treatment were positioned with the aid of a "cap" made from steel bands.



Brain Tumor

Tinea Capitis - Israel

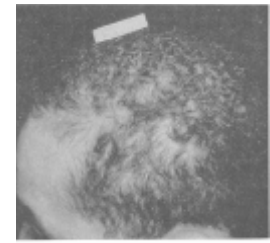


Figure 2—Gross total resection.

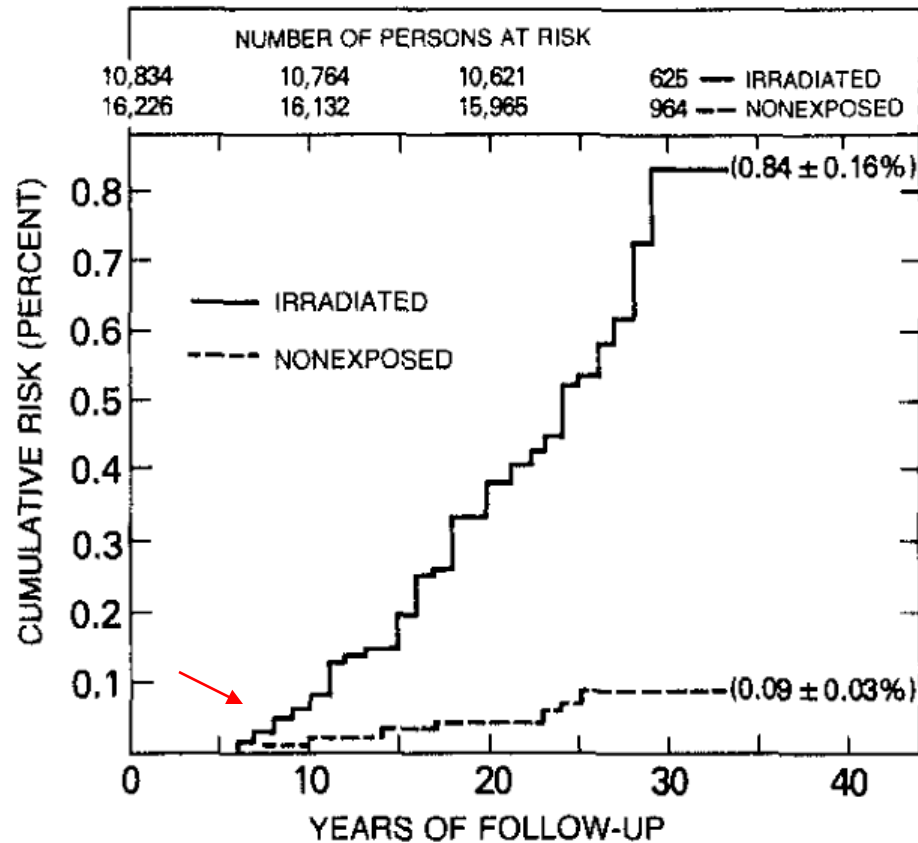
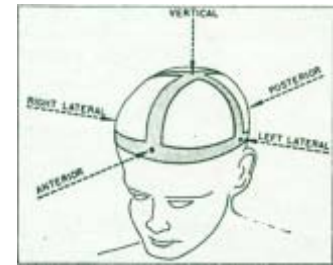
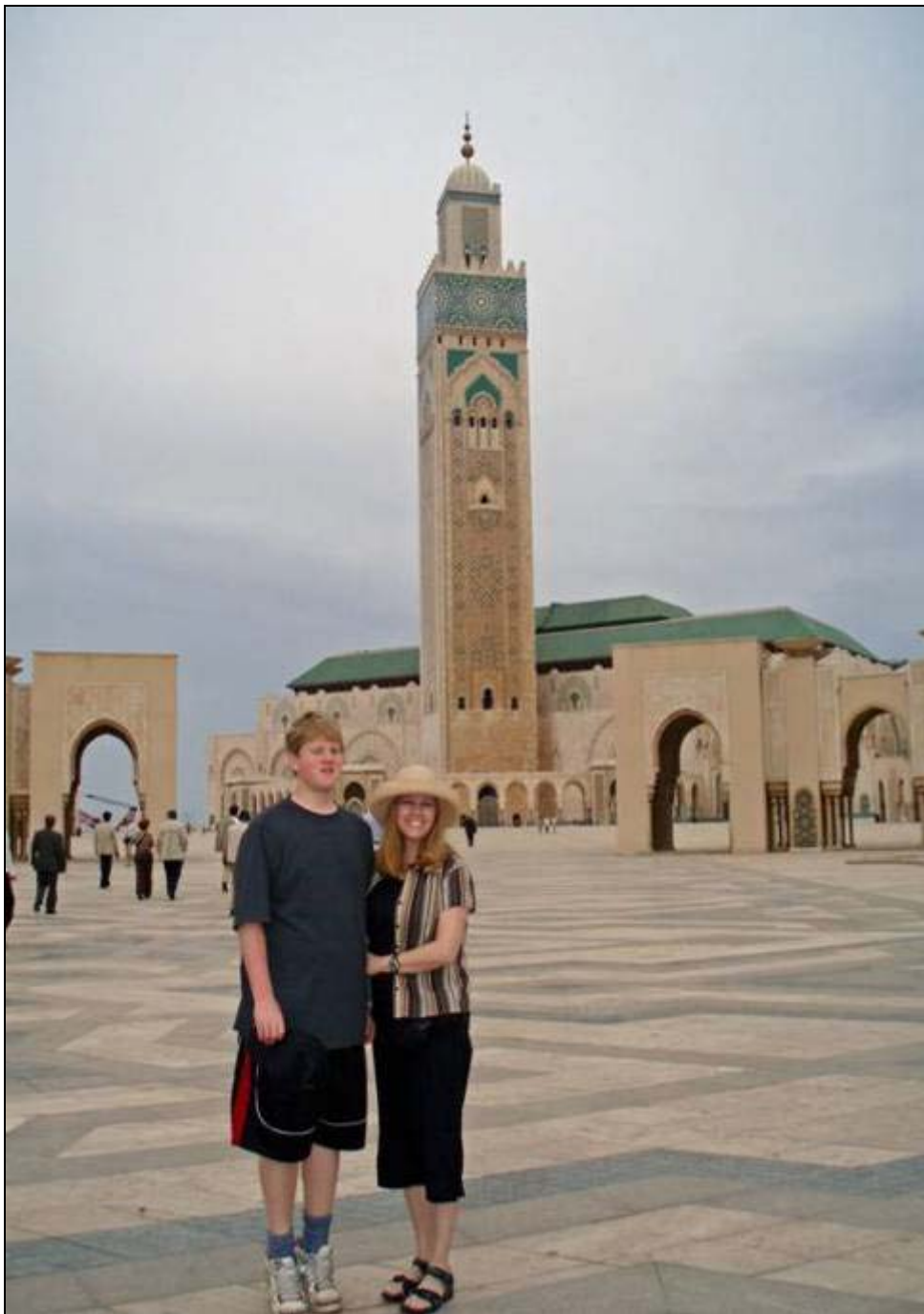


Figure 1. Cumulative Risk of Neural Tumors among Irradiated Subjects, as Compared with the Combined Control Groups.

Thyroid Tinea Capitis - Israel

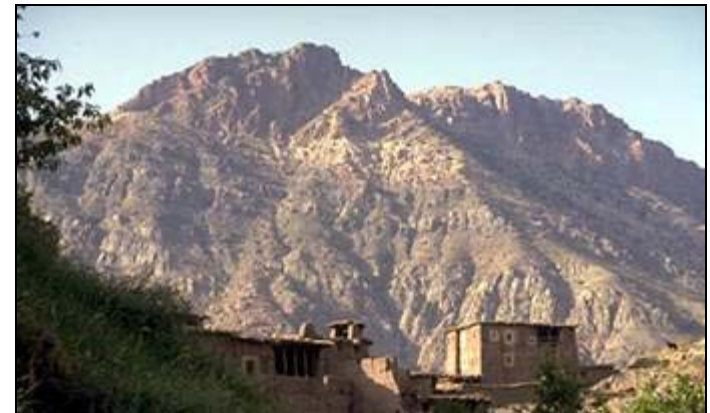


Number Exposed:	10,834
Number Nonexposed:	16,226
Thyroid Dose (mean):	9 cGy
Observed Thyroid Cancers:	43
Expected:	10.7
RR (95% CI):	4.0 (2.3 - 7.9)



Some **Uncertainties of Epidemiology...**

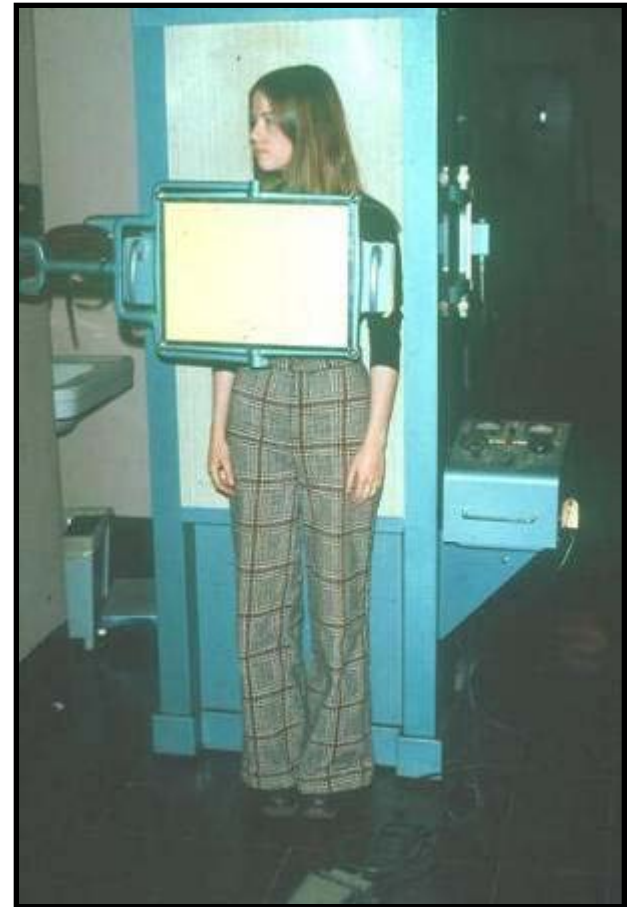
- Effect primarily among immigrants, mainly from **Morocco**, not Israeli born (Ron, *Rad Res*, 1989)
- “Irradiation for tinea capitis was given to many Jews in **Morocco** prior to immigration...” (Modan, *JNCI*, 1980)
- **Genetic susceptibility** & family clustering (4 sisters thyroid disease)
- **Wiggle** could increase dose x 3
- Immigrants from Morocco came from Atlas Mt region, and **diets** deficient in stable iodine





Studies of Low-Dose Exposures Accumulating to High Dose

Lung collapse therapy for
tuberculosis and associated
multiple chest fluoroscopic
x-rays (1930-1954)



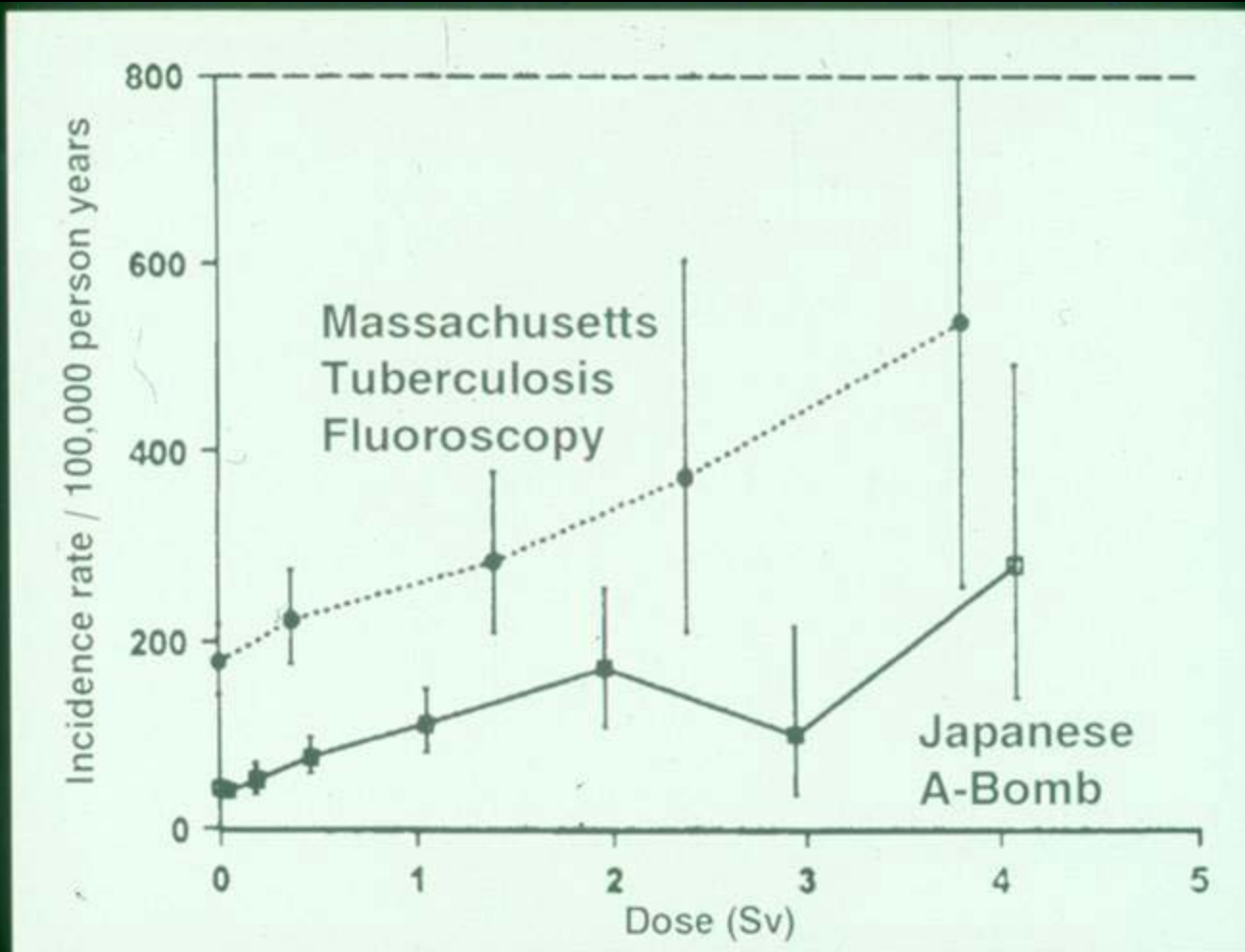
Breast Cancer TB - Fluoroscopy, Massachusetts

	Exposed	Nonexposed
No. of women	2,573	2,367
No. chest fluoroscopies (ave)	88	--
Dose (ave) [<i>Dale Trout</i>]	79 cGy	--
Breast cancers		
Observed (O)	147	87
Expected (E)	114	101
O/E	1.29	0.86
29% Excess		

Boice et al, *Radiat Res* 126:214, 1991
Boice & Monson, *J Natl Cancer Inst* 59:823 1977



Breast Cancer Incidence – Dose Response

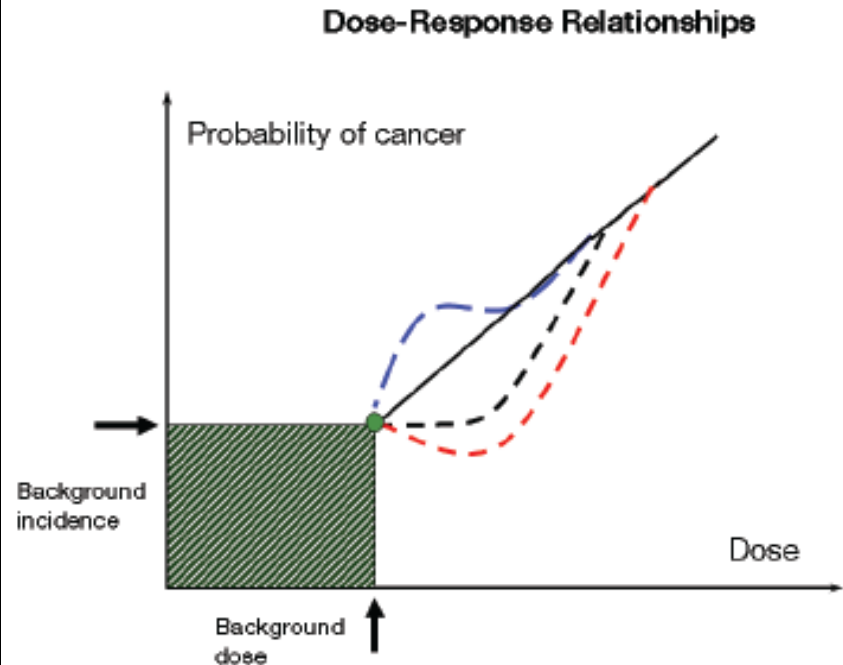


Little & Boice, *Radiat Res* 151:218, 1999

LNT – Plausible and Practical

Although Risk Below 100 mSv Uncertain

(67) ... the adoption of the LNT model combined with a judged value of a dose and dose rate effectiveness factor (DDREF) provides a prudent basis for the practical purposes of radiological protection, i.e., the management of risks from low-dose radiation exposure. (ICRP Publ 103, 2007)



Low Dose and
Low Dose-Rate Radiation
Effects and Models

Lung and Leukemia

TB - Fluoroscopy, Massachusetts



	Lung	Leukemia
No. exposed	6,285	6,285
No. unexposed	7,100	7,100
No. chest fluoroscopies (ave)	77	77
Dose to lung or marrow	84 cGy	9 cGy
Observed (O)	69	17
Expected (E)	86	19
RR (95% CI)	0.8 (0.6-1.0)	0.9 (0.5-1.8)

No excess lung or leukemia

Not all tissues respond similarly to fractionation.

Lung TB - Fluoroscopy, Canada Compared with Japanese LSS

	Multiple Fluoroscopy		Atomic Bomb	
Lung Dose (cGy)	# Lung Ca	RR (95% CI:)	# Lung Ca	RR (95% CI:)
< 1	723	1.0	248	1.0
1 -	180	0.87 (0.7-1.0)	290	1.26 (1.1-1.5)
50 -	92	0.82 (0.7-1.0)	38	1.45 (1.0-2.1)
100 -	114	0.94 (0.8-1.2)	30	1.93 (1.3-2.9)
200 -	41	1.09 (0.8-1.5)	10	2.65 (1.5-4.7)
300+	28	1.04 (0.7-1.5)	3	--
ERR/Gy (95% CI)	0.00 (-0.06–0.07)		0.60 (0.27–0.99)	

Howe G, *Radiat. Res.* 1995; 142:295

Heart Disease

TB – Fluoroscopy, Massachusetts



Number exposed 6,285

Number unexposed 7,100

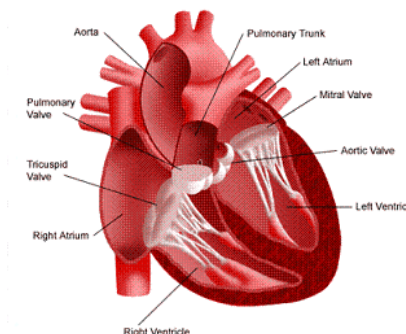
Heart dose (ave) ~90 cGy

Chest fluoroscopies (ave) ~ 77

Observed heart disease (O) 826

Expected (E) 908

RR (95% CI) **0.9** (0.8-1.0)





Leukemia Incidence Swedish I-131 Studies

	Diagnostic I-131	Hyperthyroidism Therapy	Cancer Therapy
No. patients	36,326	9,860	802
Mean bone marrow dose (cGy)	0.02	4.8	25.1
Non-CLL			
No. cases	103	25	2
SIR	1.2	0.8	1.2
95% CI	(0.95-1.4)	(0.6-1.2)	(0.2-4.4)

Thyroid Cancer

Swedish Diagnostic I-131 (Scans)

Number Exposed:	24,010
Years of Scans	1952-69
Thyroid Dose:	0.94 Gy (94 rad)
Observed Thyroid Cancer:	36
Expected:	39.5
RR (95% CI)	0.9 (0.6 - 1.3)

Dickman et al, *Int J Cancer*, 106:580, 2003

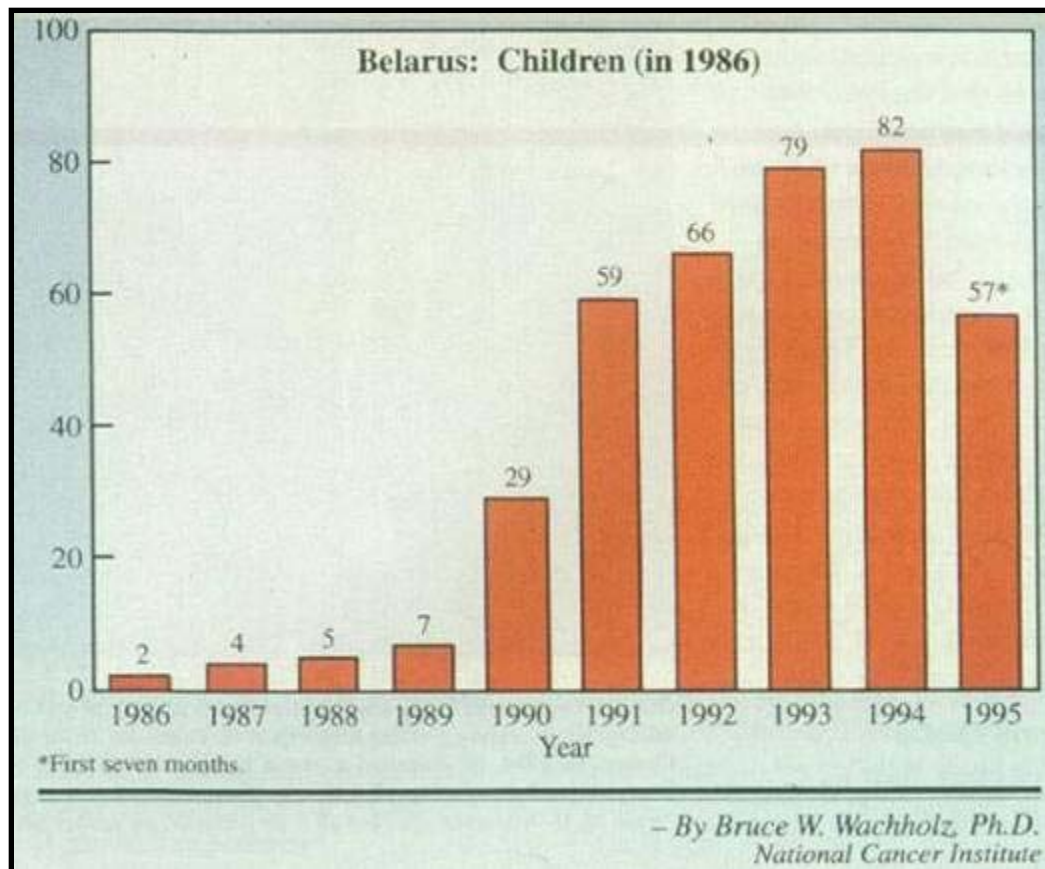
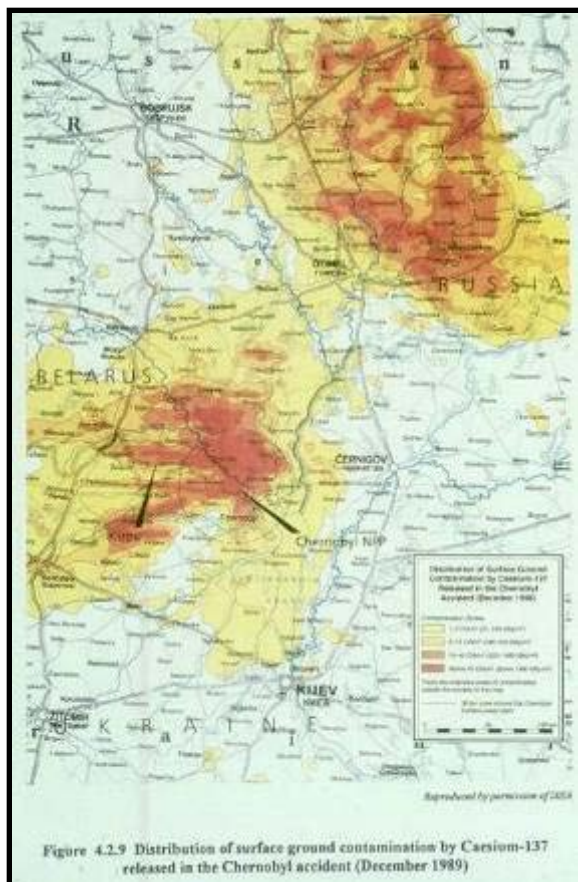
Hall et al, *Radiat Res*, 145:86, 1996

Hits (1980 - 1990s)

- Chernobyl
- Hanford
- Mayak
- Hodgkin Lymphoma
- Retinoblastoma
- Childhood Cancer
- Rocketdyne (Atomics International)



Thyroid Cancers in Children in Belarus



Belarus Milk
Japanese children - Fukushima
Washington State

Thyroid Cancer (IARC 2005)

Risk Varies by KI and Endemic Goiter

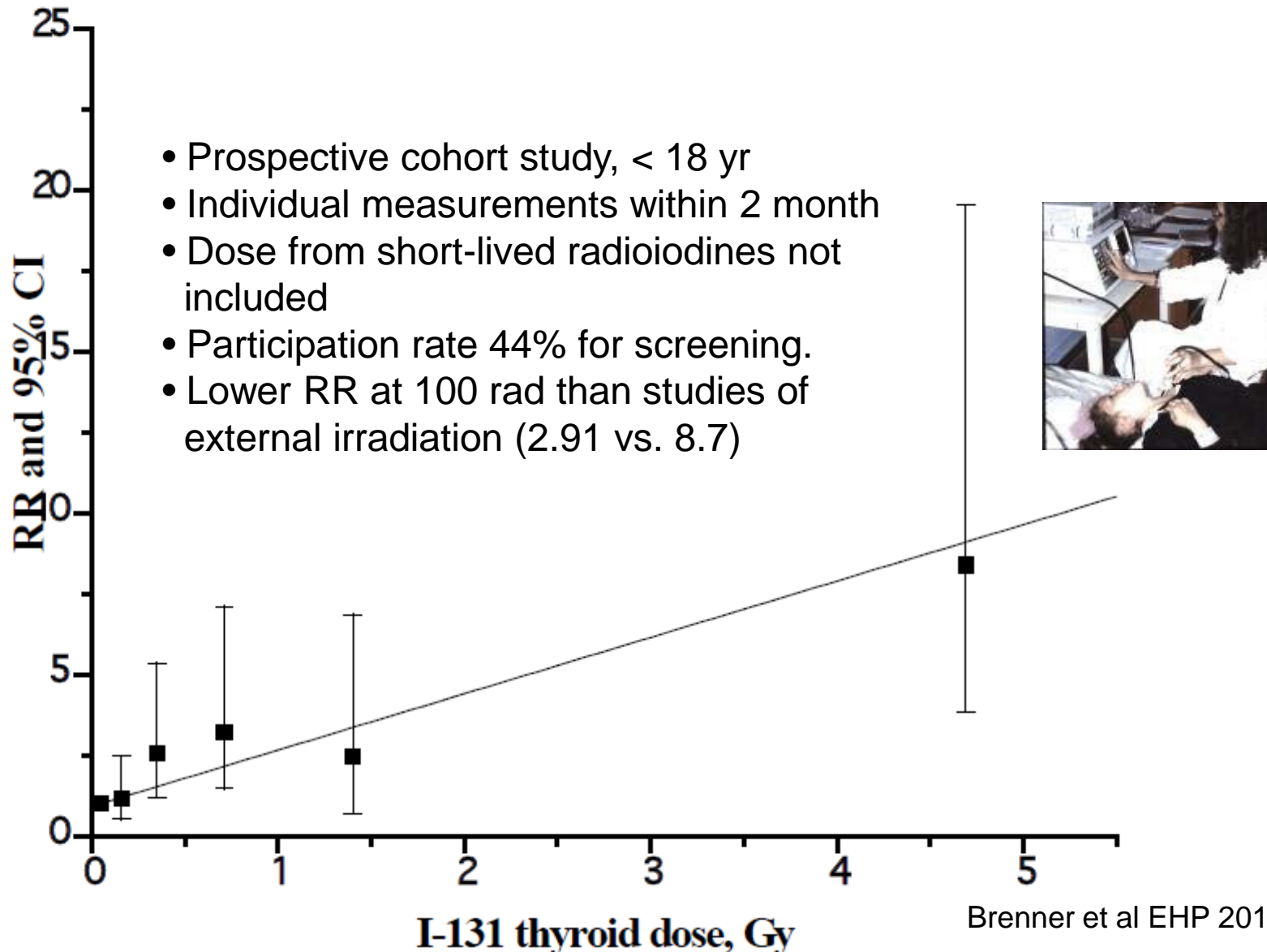
Consumption of potassium iodide	RR at 100 rad (95% CI)	
	Highest two tertiles of soil iodine	Lowest tertile of soil iodine
No	3.5 (1.8 to 7.0)	10.8 (5.6 to 20.8)
Yes	1.1 (0.3 to 3.6)	3.3 (1.0 to 10.6)

Lower risk seen among children with normal levels of stable iodine in diet.

Cardis *et al.* *JNCI* 97:724, 2005



Ukrainian – American Thyroid Study



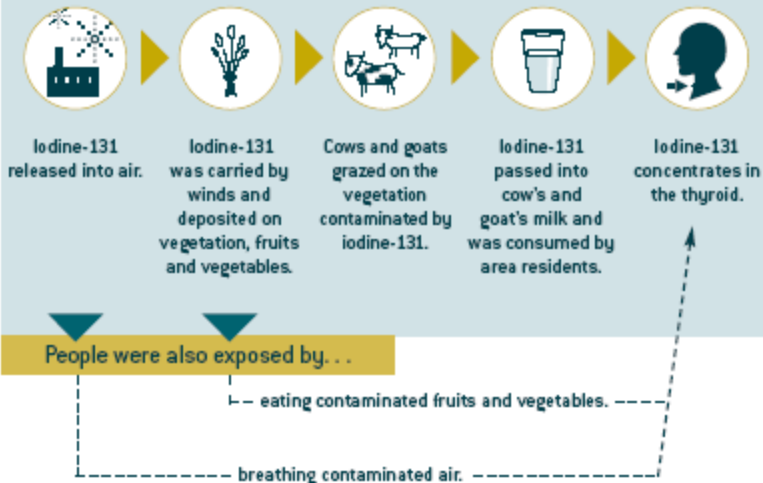


Hanford Thyroid Disease Study

FINAL REPORT

HOW WERE PEOPLE EXPOSED TO IODINE-131 FROM HANFORD?

Most people received most of their dose from contaminated milk.



THYROID GLAND

The thyroid gland is butterfly-shaped, with two lobes about the size of teaspoons. It is located in the front of the neck, below the Adam's apple.

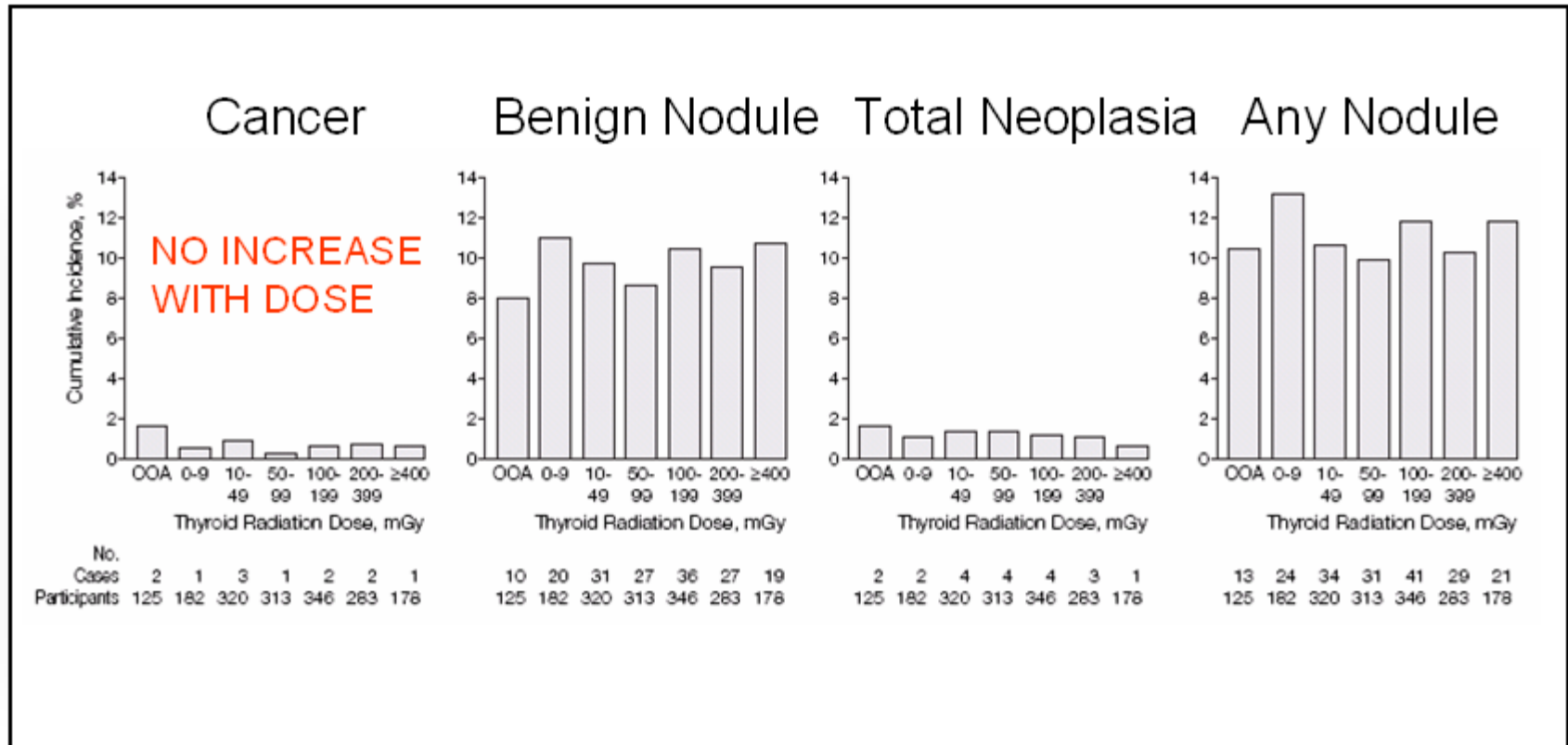


Davis S, Kopeccky KJ, Hamilton TE. Hanford Thyroid Disease Study. Final Report. 2002. Fred Hutchinson Cancer Research Center, Seattle, WA. (CDC Contract No. 200-89-0716), June 21, 2002 (Available at: <http://www.cdc.gov/nceh/radiation/hanford/htdsweb/pdf/htdsreport.pdf>)

Hanford Thyroid Disease Study

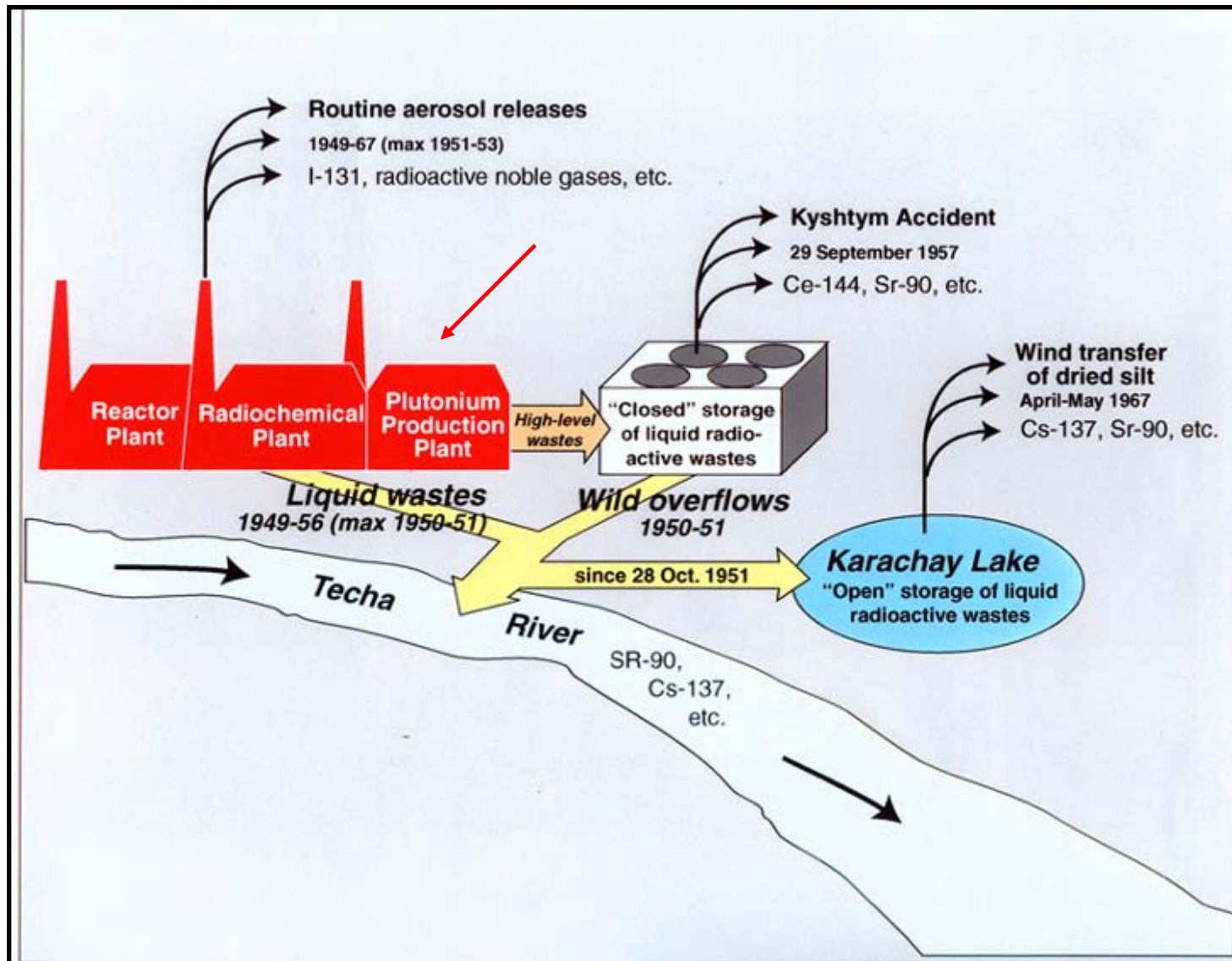
- Exposure 1944-1957 (“pure” I-131)
- About 5,200 births in 1940-1946 selected
- 3,440 examined 1992-97
- Dose Reconstruction (17.4 rad ave.; <1-100+ rad range)

Cumulative Incidence of Thyroid Disease by Dose

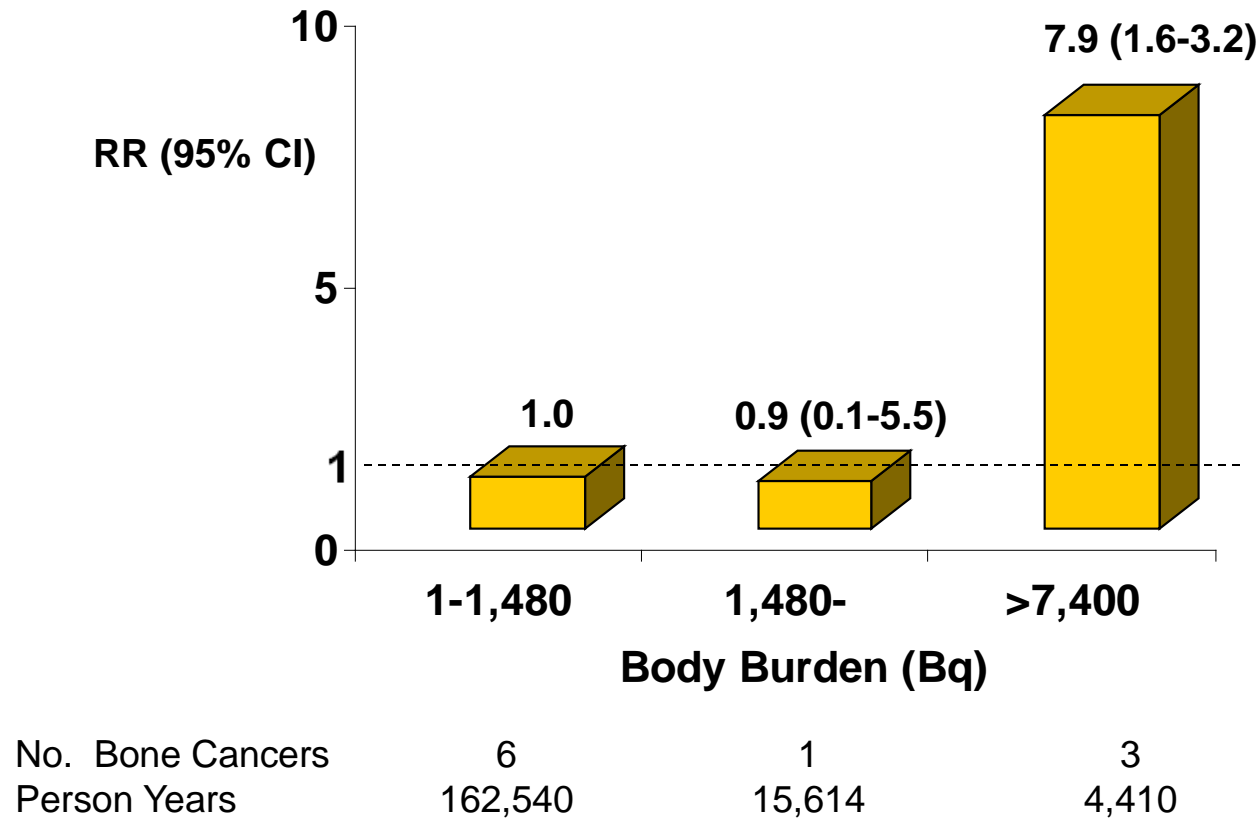


The percentage of people with thyroid disease is the same, regardless of dose.

Mayak Nuclear Weapons Plant



Mayak - Plutonium - Bone

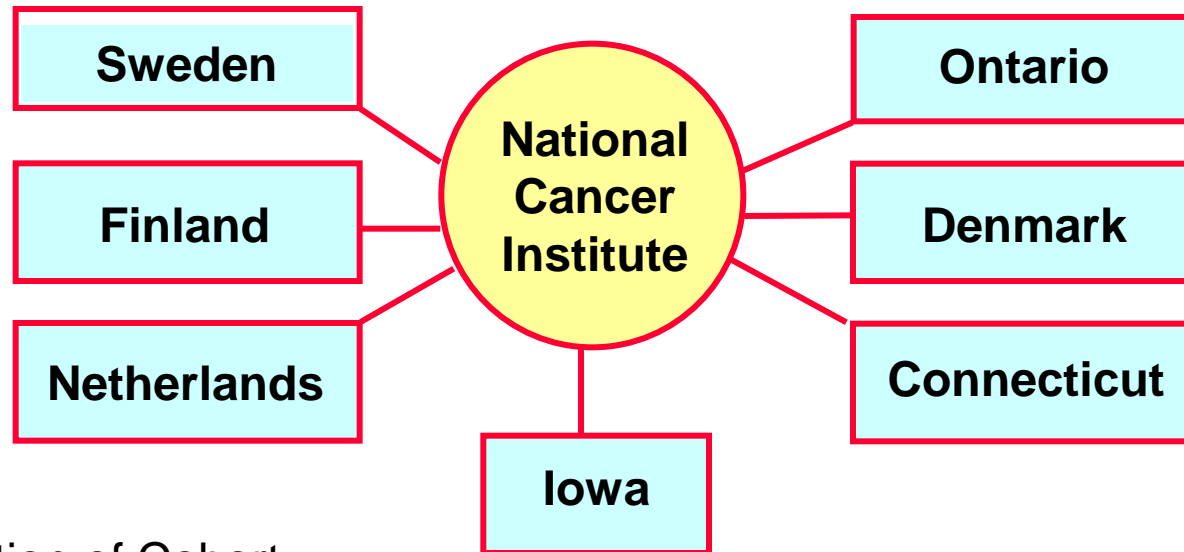


Gilbert et al, *Radiat Res* 154:237, 2000

Alpha emitter, Bone threshold?
No leukemia excess.

Lung Cancer Following Hodgkin Lymphoma

International Case - Control Study (2002)



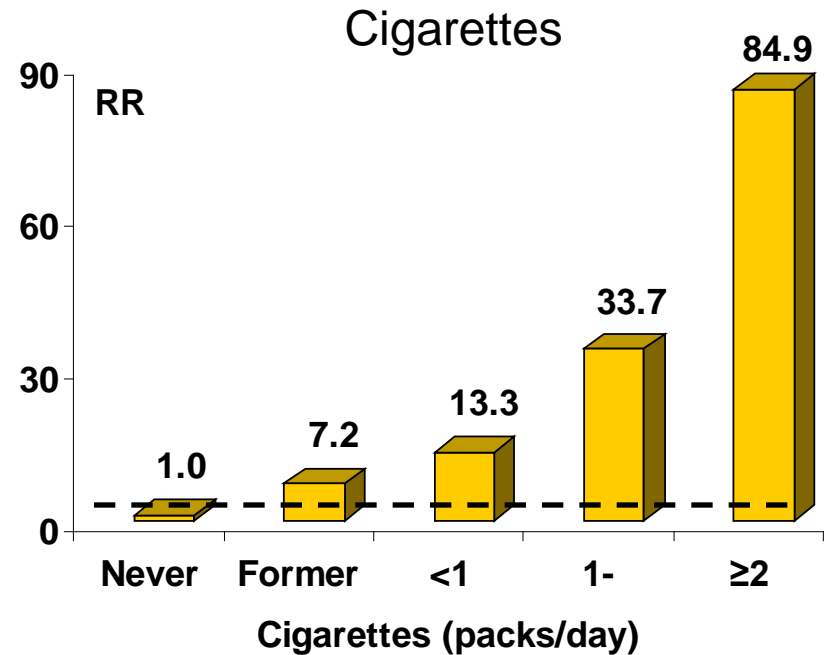
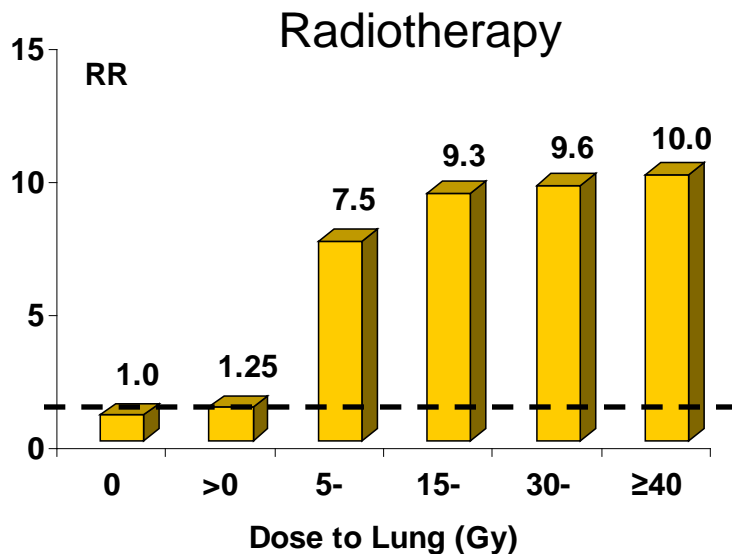
Definition of Cohort:

- Diagnosis of Hodgkin lymphoma: 1965-1994
- Survival of 1 or more years

Final Cohort: 22,977 (222 cases, 444 controls)

Travis et al. *JNCI* 94:182, 2002

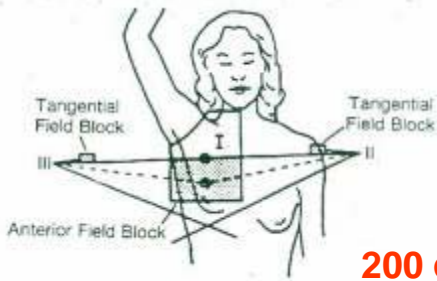
Lung Cancer After Hodgkin Lymphoma Radiotherapy and Environmental Factors



<1 pack/day has greater risk than ≥40 Gy

Gilbert et al, *Rad Res* 159:161, 2003

Travis et al, *JNCI* 94:182, 2002



200 cGy (ave)

Radiotherapy for Breast Cancer

All Breast Cancers in Connecticut (1935-82)

Second Breast Cancer

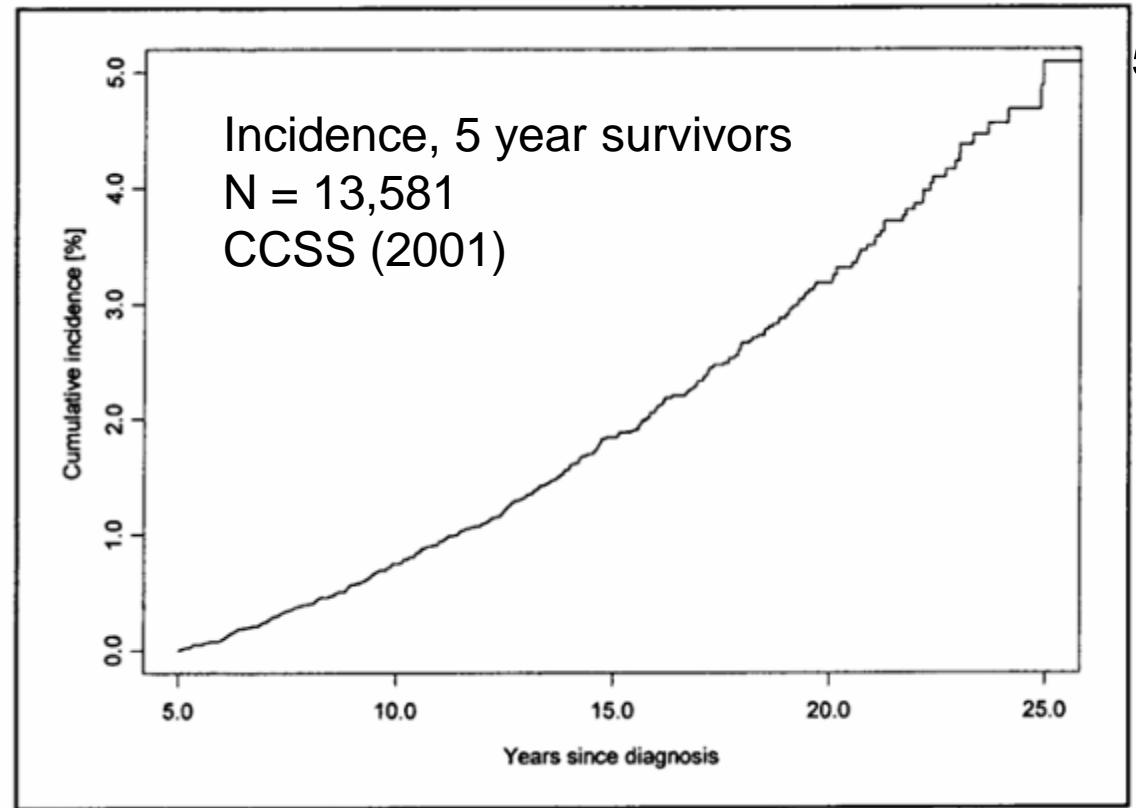
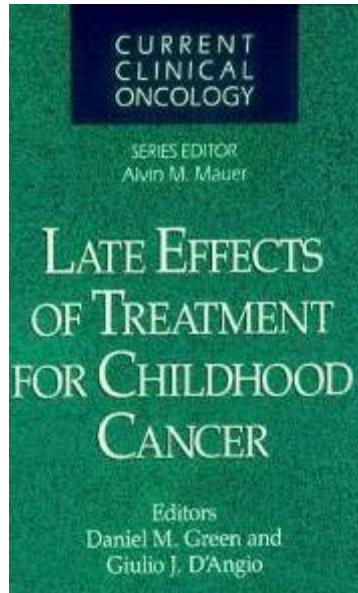
	RR	95% CI
All Subjects*	1.19	0.9-1.5
Time After Exposure (Yr)		
5-9	0.99	0.7-1.4
≥10	1.33	1.0-1.8
Age at Exposure (Yr)		
<35	2.26	0.9-5.7
35 -	1.46	0.9-2.3
≥45	1.01	0.8-1.4

*655 Cases, 1,189 Controls

Boice et al, *NEJM* 326:781, **1992**

Risk after 10 years among young.
Example of age modification.

2nd Cancers After Childhood Cancer (CCSS)

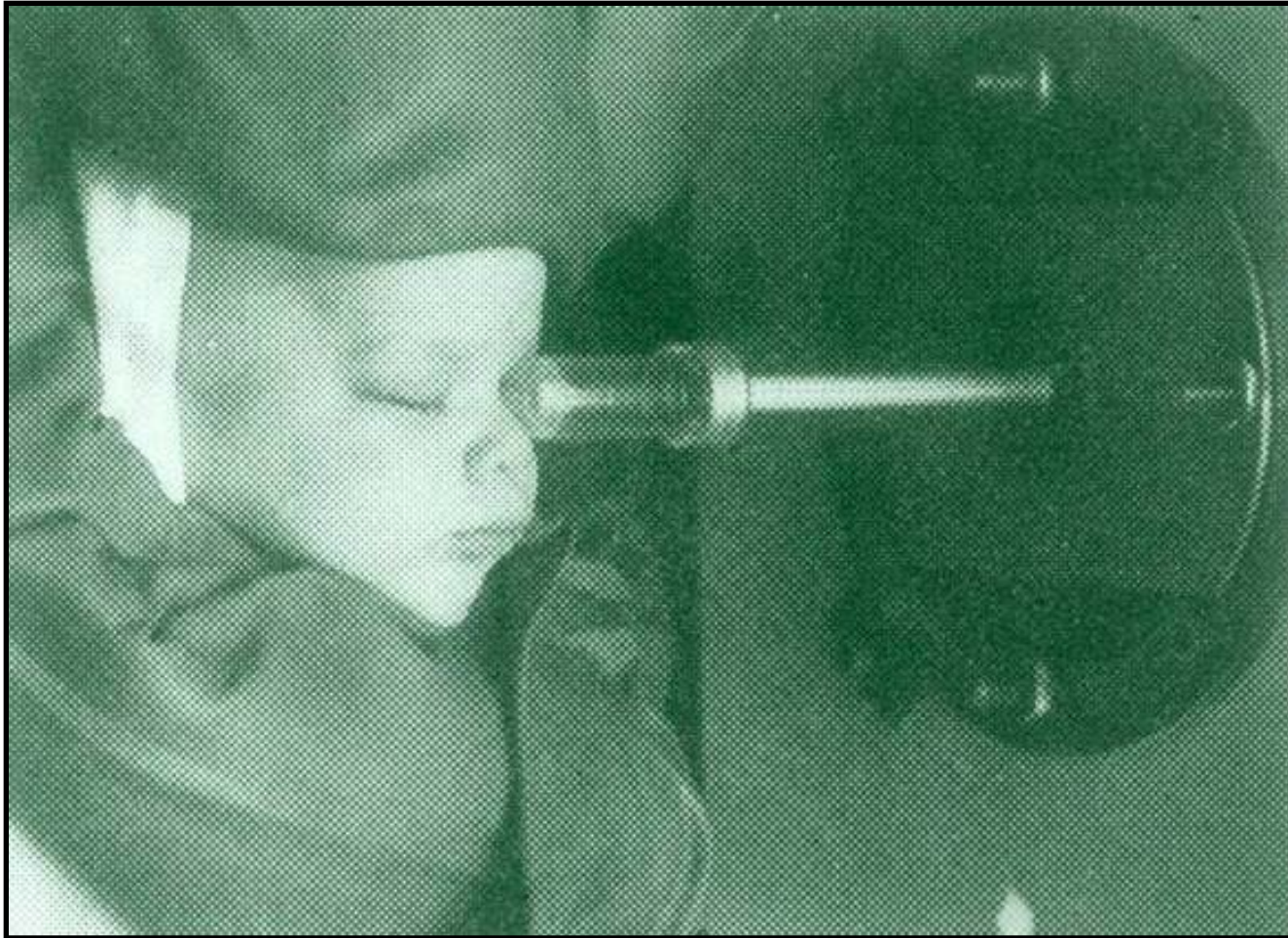


5%

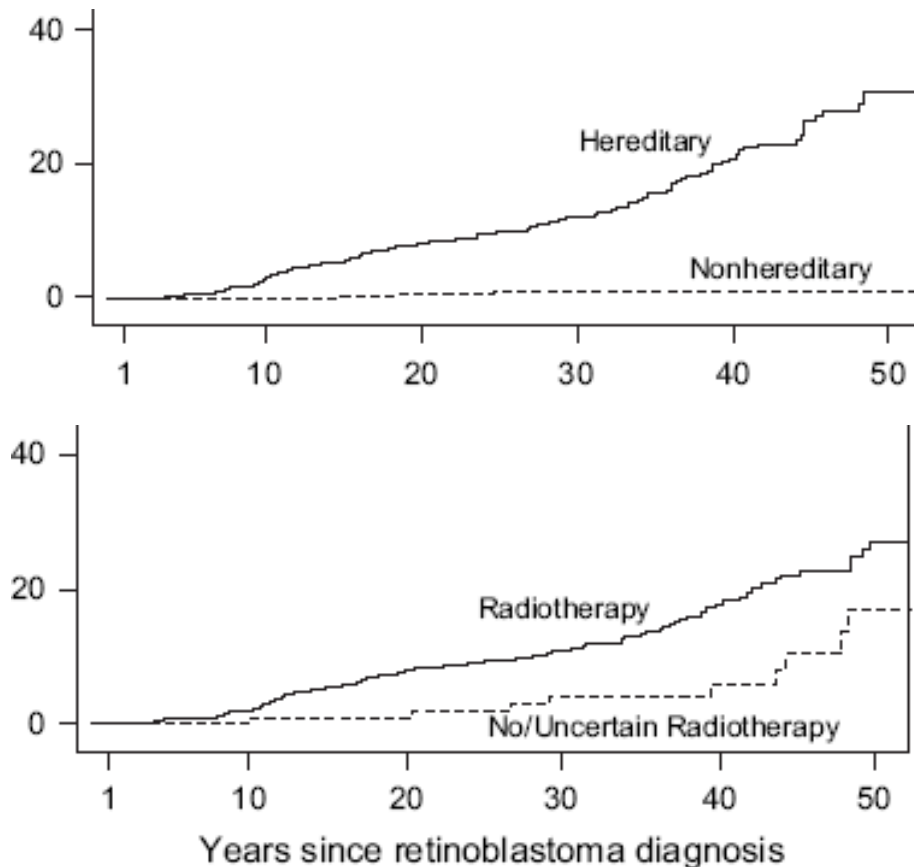


Neglia, *JNCI* 93:618, 2001

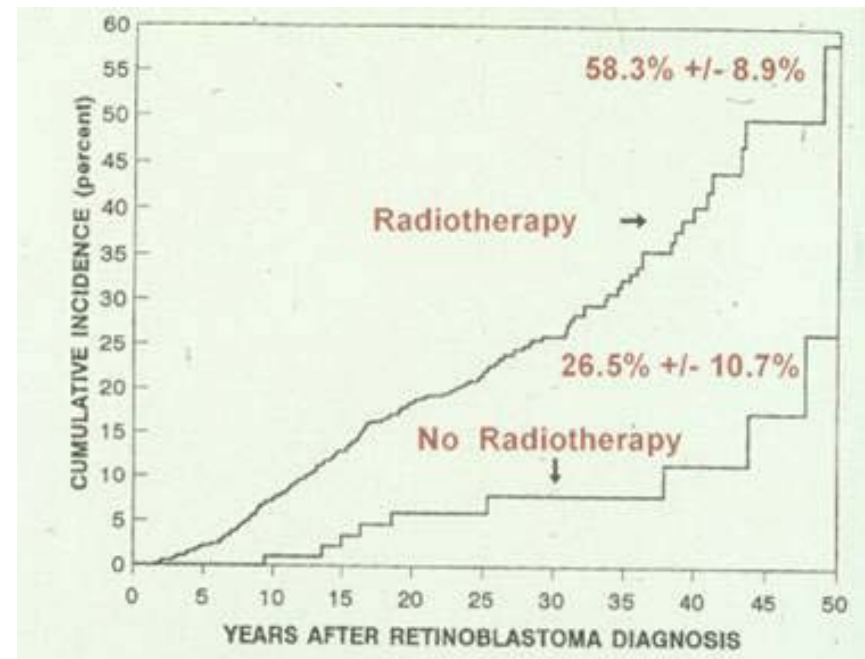
Early Treatment of Retinoblastoma



Second Cancer after Retinoblastoma



Possible high dose interaction with genetic susceptibility



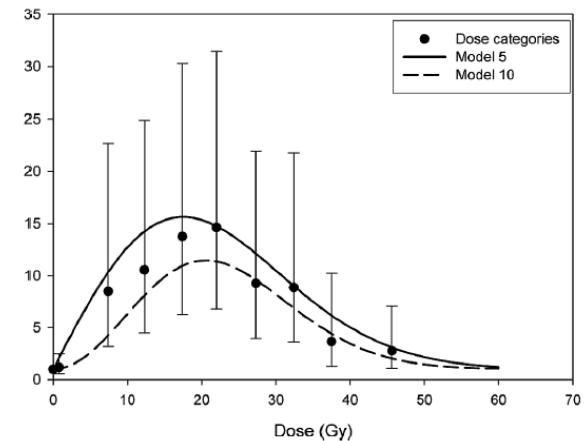
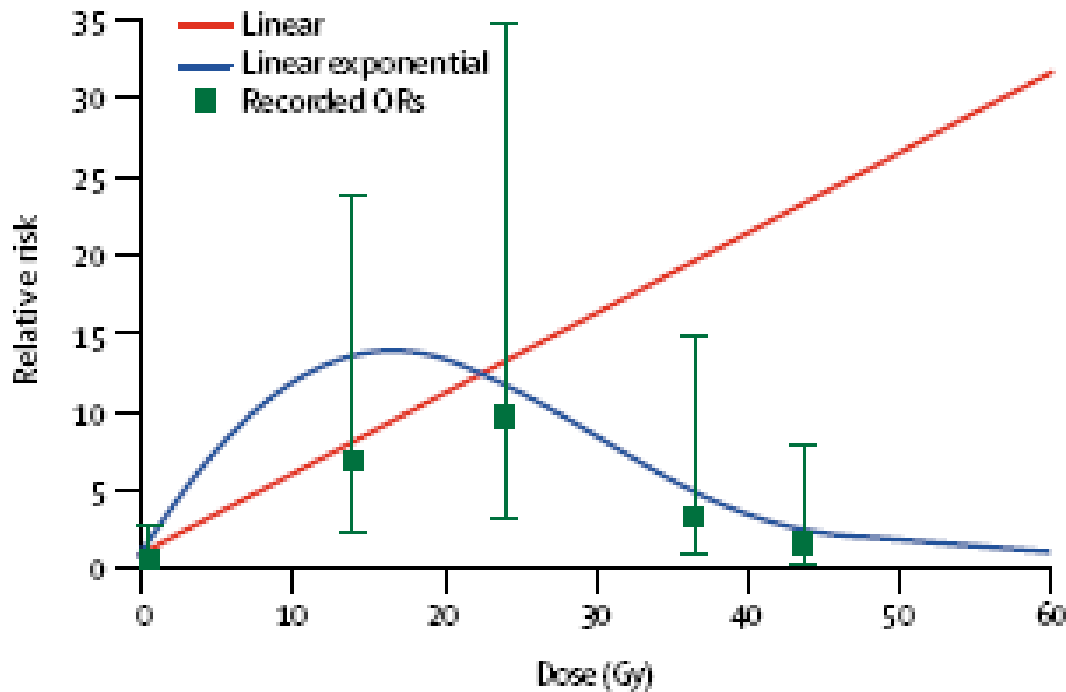
Updated. Yu et al.
JNCI 101:581, 2009

Updated. Kleinerman et al.
JCO 23:2272, 2005

Wong et al.
JAMA 278:1262, 1997

Thyroid Cancers After Childhood Cancer (CCSS)

Cell Killing



Sigurdson, *Lancet* 365:2014, 2005
Tucker, *Cancer Res* 51:2885, 1991
Meadows, *JCO* 27, 2009
Bhatti, *Rad Res* 174, 2010

Radiation Dose and Breast Cancer Risk in the Childhood Cancer Survivor Study

Peter D. Inskip, Leslie L. Robison, Marilyn Stovall, Susan A. Smith, Sue Hammond, Ann C. Mertens, John A. Whitton, Lisa Diller, Lisa Kenney, Sarah S. Donaldson, Anna T. Meadows, and Joseph P. Neglia

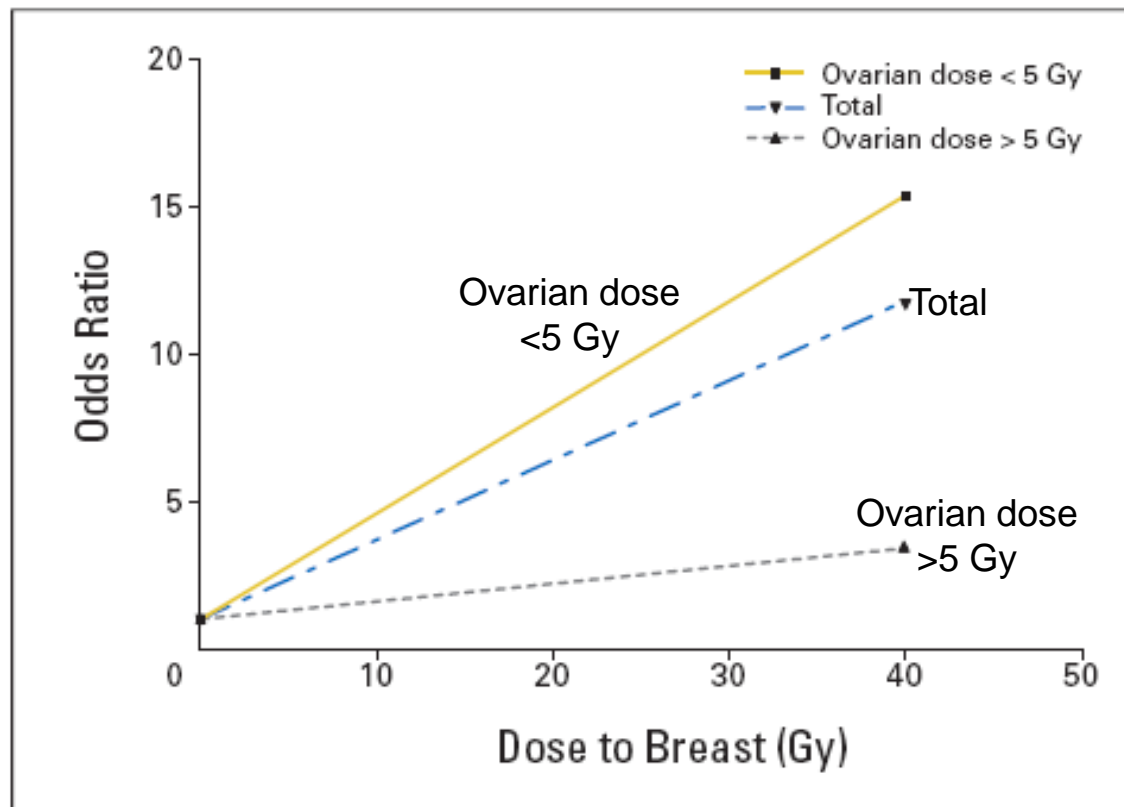
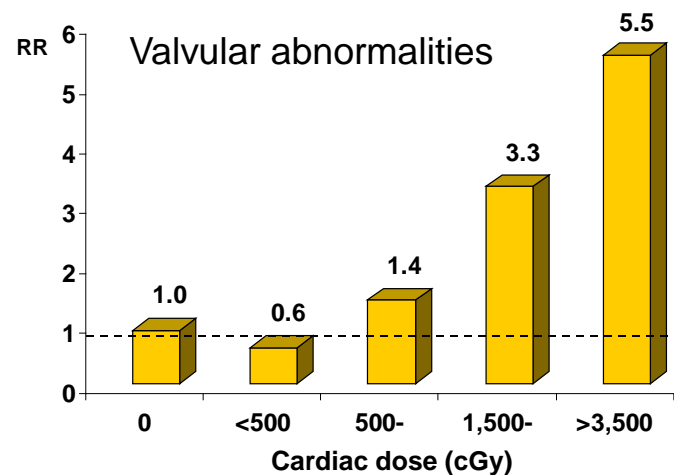
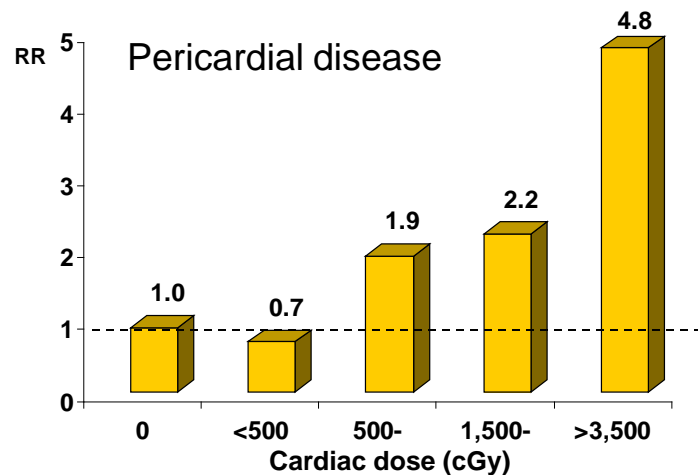
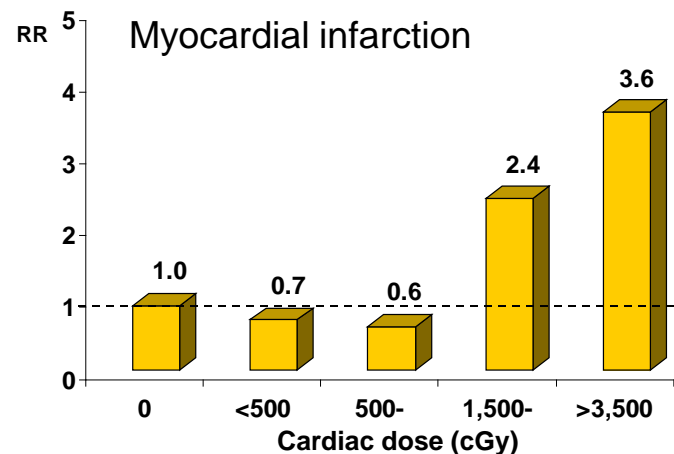
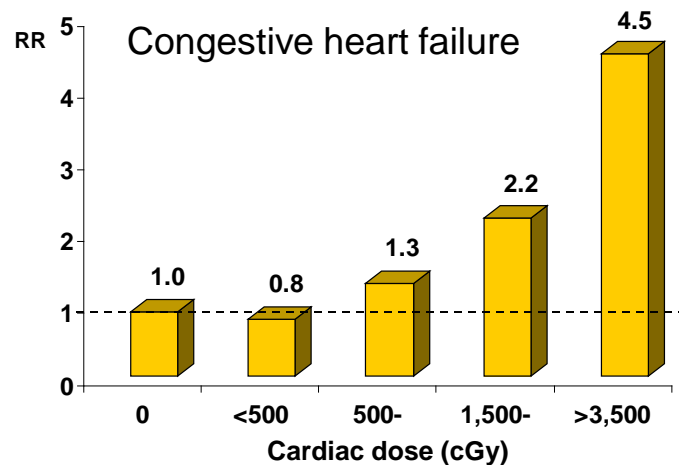


Fig 2. Fitted breast cancer risk by radiation dose to the breast and ovary.

Competing effect of
ovarian dose and
radiation induced
early menopause --
Host factor influence

Inskip, JCO 27, 2009

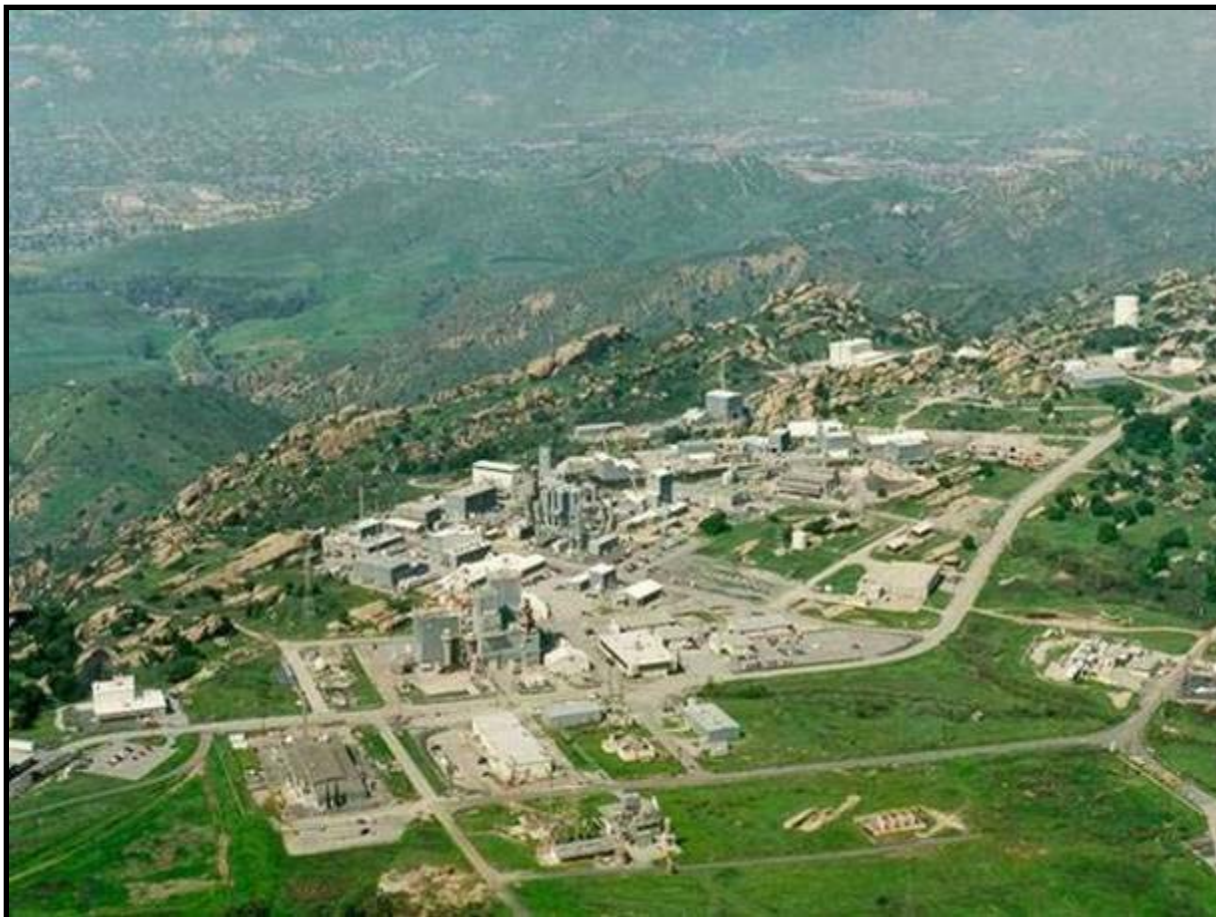
Dose Response – Heart Disease (CCSS)



Radiation Worker Studies

Rocketdyne – Atomics International

Santa Susana Field Laboratory



Endeavor Space
Shuttle last launch
May 16, 2011

Leggett et al. J Radiol Prot 2005
Boice et al. Health Physics 2006

Boice et al. Radiat Res 2006
Boice et al. Radiat Res 2011 (in press)

Sodium Reactor Experiment - 1956



First commercial power reactor – provided electricity for Moorpark.

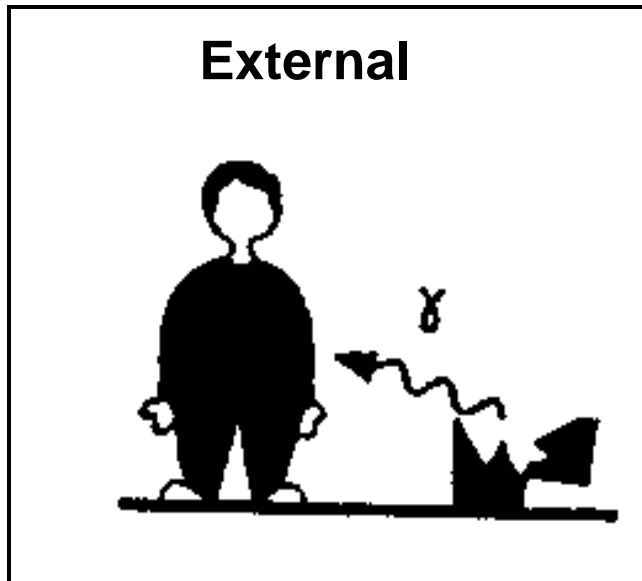
20 MWt. July 1959, partial meltdown; restarted Sep 1960 until 1964.

For one hour on November 12, 1957 this fact was featured on Edwin R. Murrow's "[See It Now](#)" prime time news - television show.

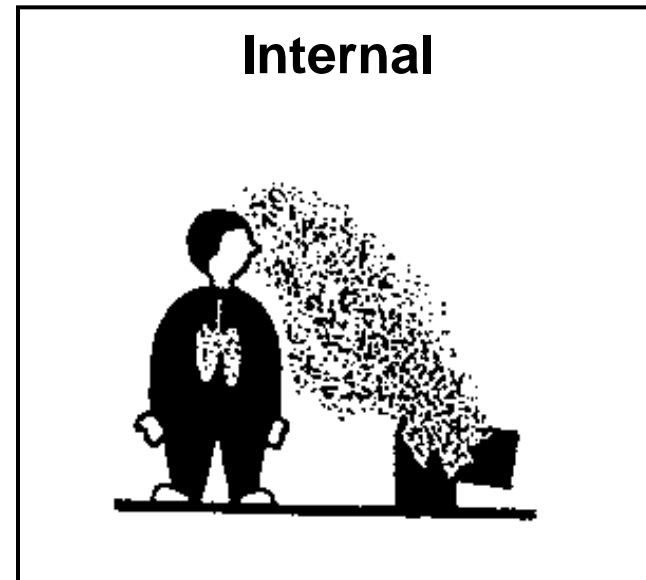
- Gamma
- X-ray (radiographers)
- Neutrons

Types of Exposure

- Uranium, Plutonium
- Americium, **Polonium**
- Thorium, Strontium
- Cesium, Tritium

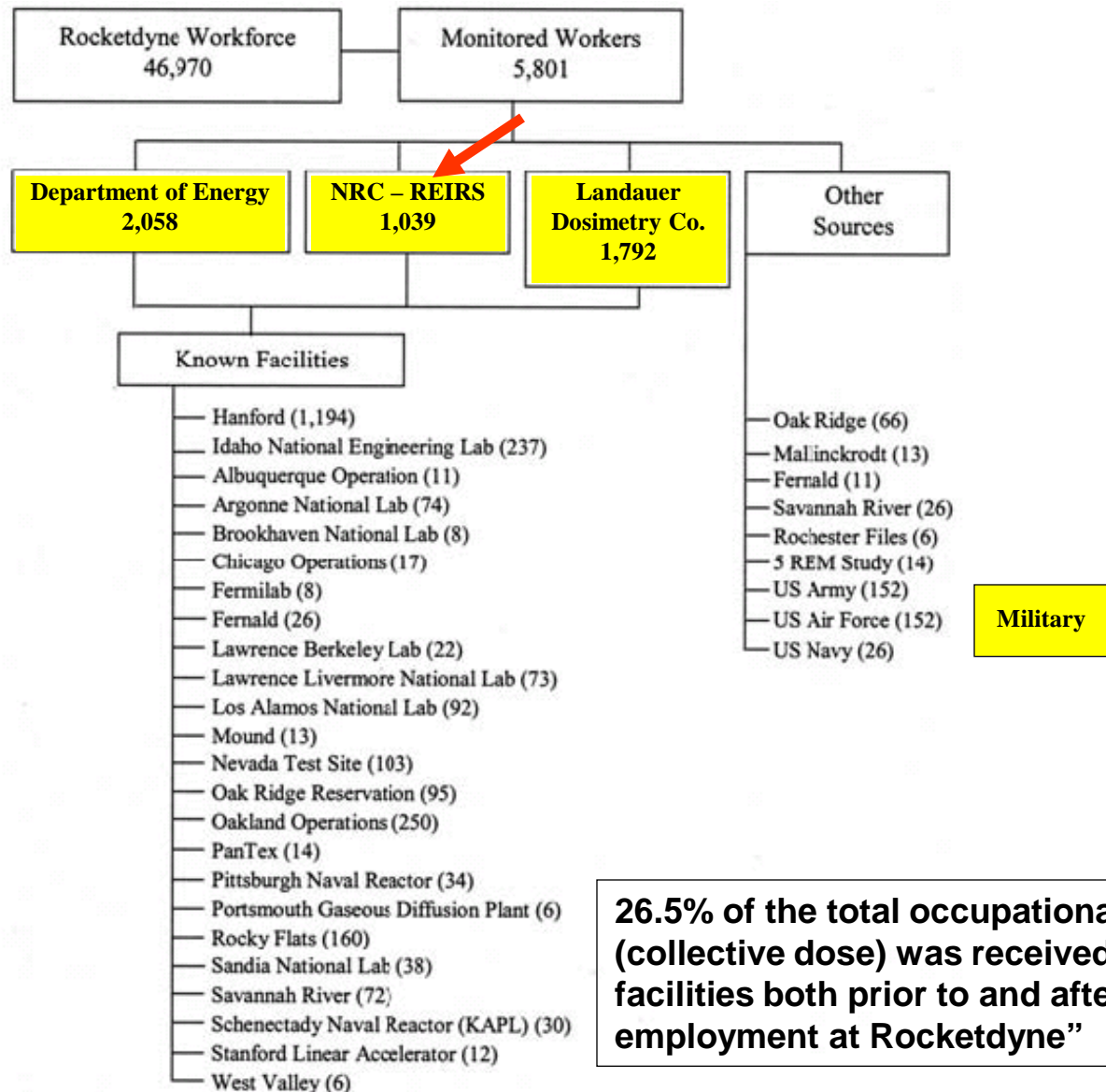


Uniform dose
Delivered during exposure
Film (TLD) badge reading



Non uniform dose
Protracted in time
Bioassay measurements

Sources of Radiation Exposure Histories



One Hit Wonders? (1990 - 2000s)

- Nuclear Facilities
- UK and International Worker Studies
- Natural Background Areas

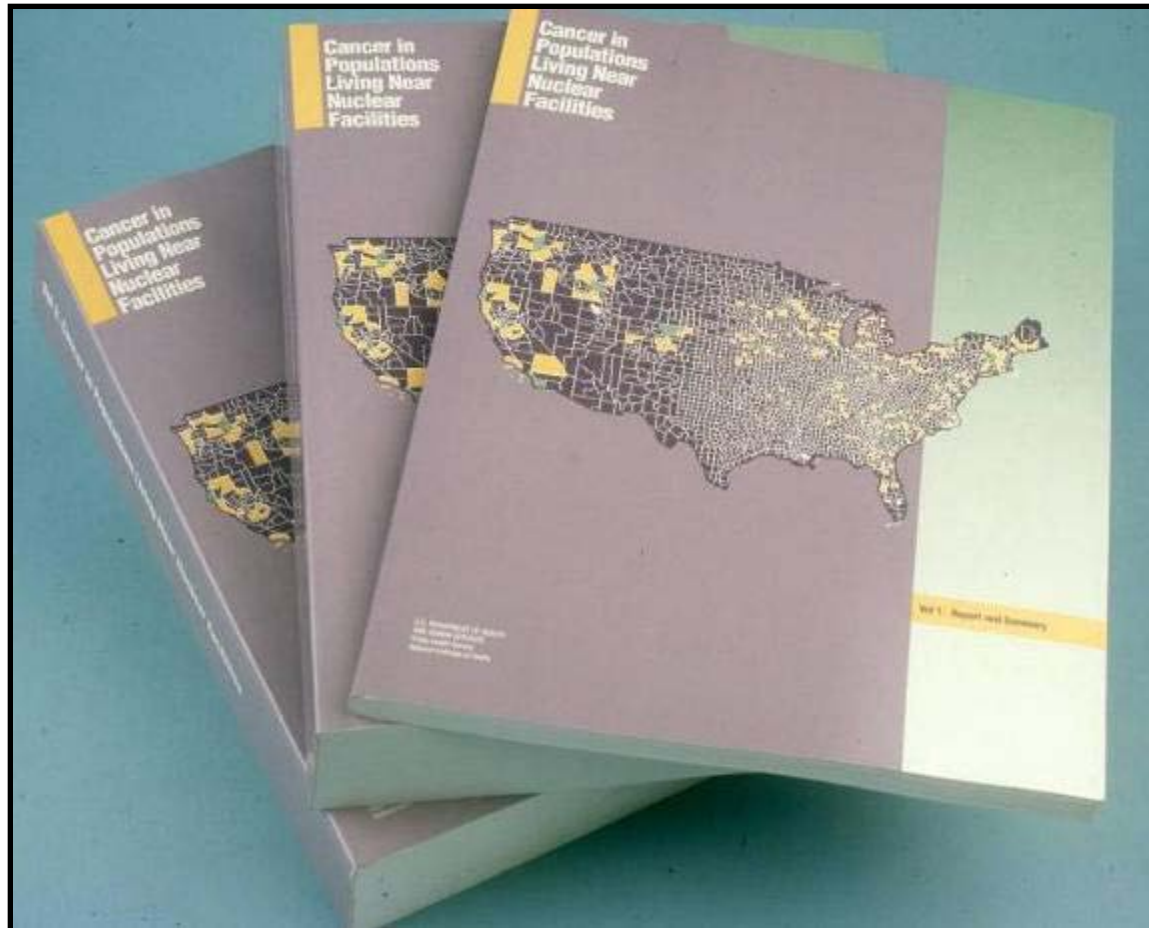


Descriptive Studies

Nuclear Facilities (Sellafield, U.K.)

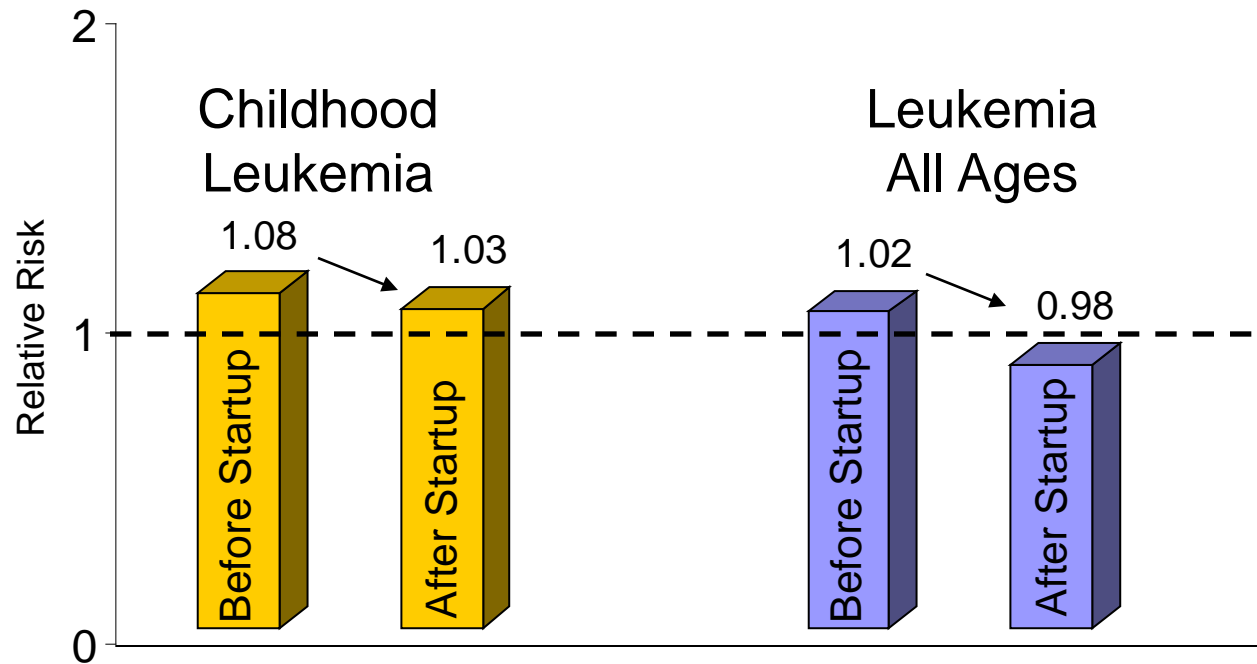


Cancer in Populations Living Near Nuclear Facilities Jablon, *JAMA* 256: 1991



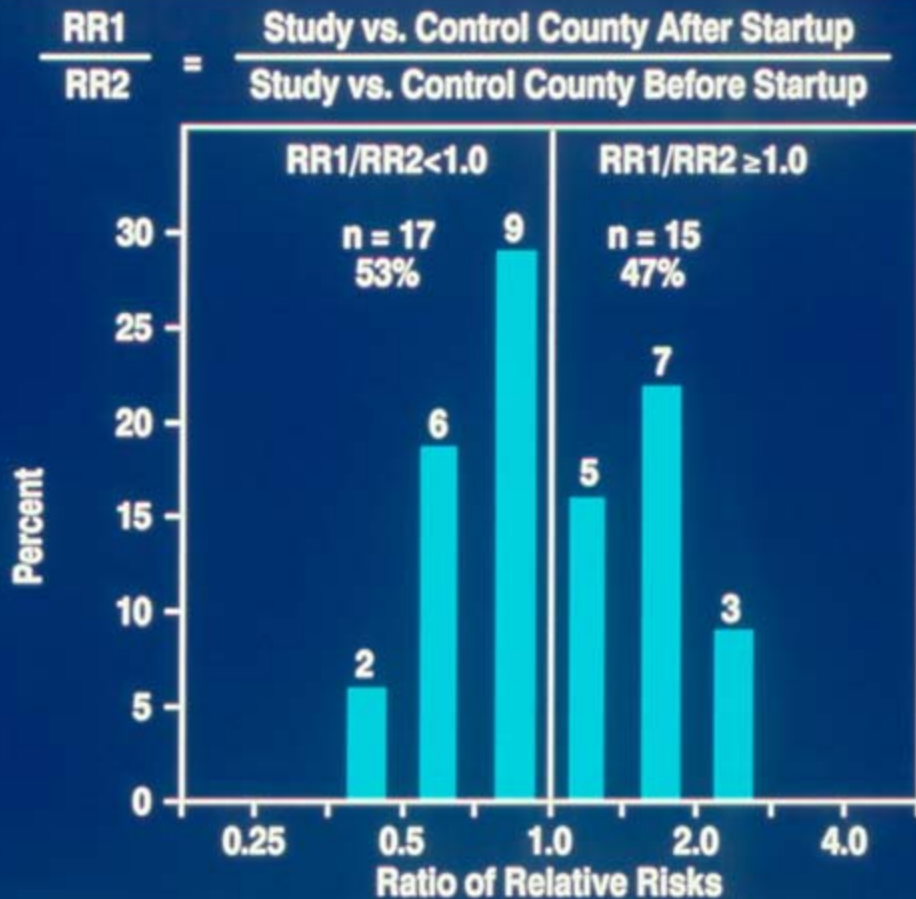
Digitally re-mastered VHS→DVD released 2011

Overall Relative Risk of Leukemia Before and After Nuclear Facility Startup



Risk higher before than after facilities began operating

Distribution of Ratios of Relative Risks^a of Childhood^b Leukemia



Concern – subgroup analyses

- multiple comparisons
- chance



COMARE 14th Report: Further consideration of the incidence of childhood leukaemia around nuclear power plants in Great Britain

6 May 2011



In this, the 14th COMARE report, the incidence of childhood leukaemia in the vicinity of nuclear power plants (NPPs) in Great Britain has been reviewed and it has been concluded that the risk estimate for childhood leukaemia associated with proximity to an NPP is extremely small, if not zero.

Figure 3.1 NPP sites in Great Britain

Epidemiology is an observational science, it is not experimental

Epidemiology is an observational science for which small biases and confounding factors become much more important at low doses.

Further, the effect to be detected at low doses is, not surprisingly, very low and the statistical power of epidemiology is insufficient to demonstrate excesses.

Low Dose Studies are More Susceptible to – Bias and Confounding and Chance

81. ... there are a number of studies of occupationally exposed persons, who generally receive low doses of ionizing radiation at low dose rates. For example, in the **IARC 15-country study**, average cumulative doses were **19.4 mSv**, and fewer than 5% of workers received cumulative doses exceeding 100 mSv. (UNSCEAR 2008)

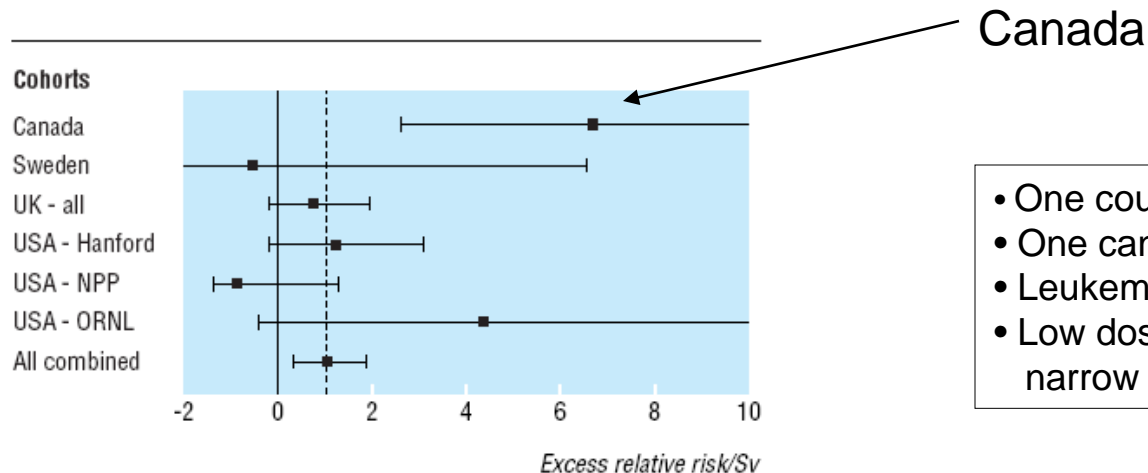


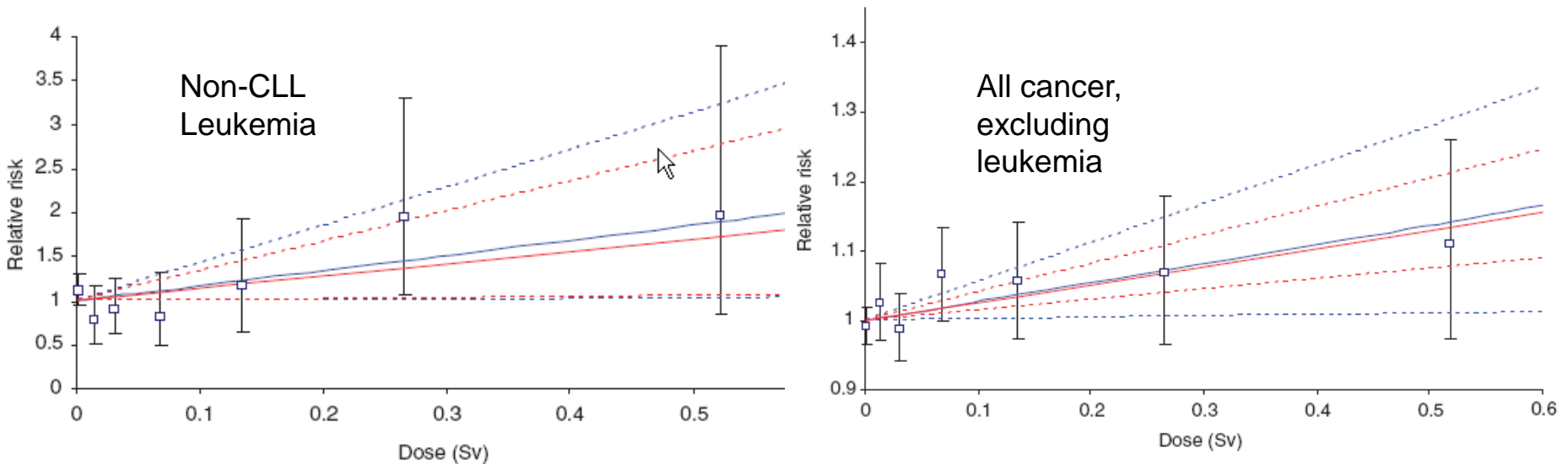
Fig 2 Excess relative risks per Sv for all cancer excluding leukaemia in cohorts with more than 100 deaths (NPP=nuclear power plants, ORNL=Oak Ridge National Laboratory)

- One country of 15 (Canada)
- One cancer of 28 (lung)
- Leukemia not significant
- Low dose (**19.4 mSv**) and narrow dose distribution

Cardis et al. BMJ 2005
Ashmore et al. JRP 2010
Boice JRP 2010

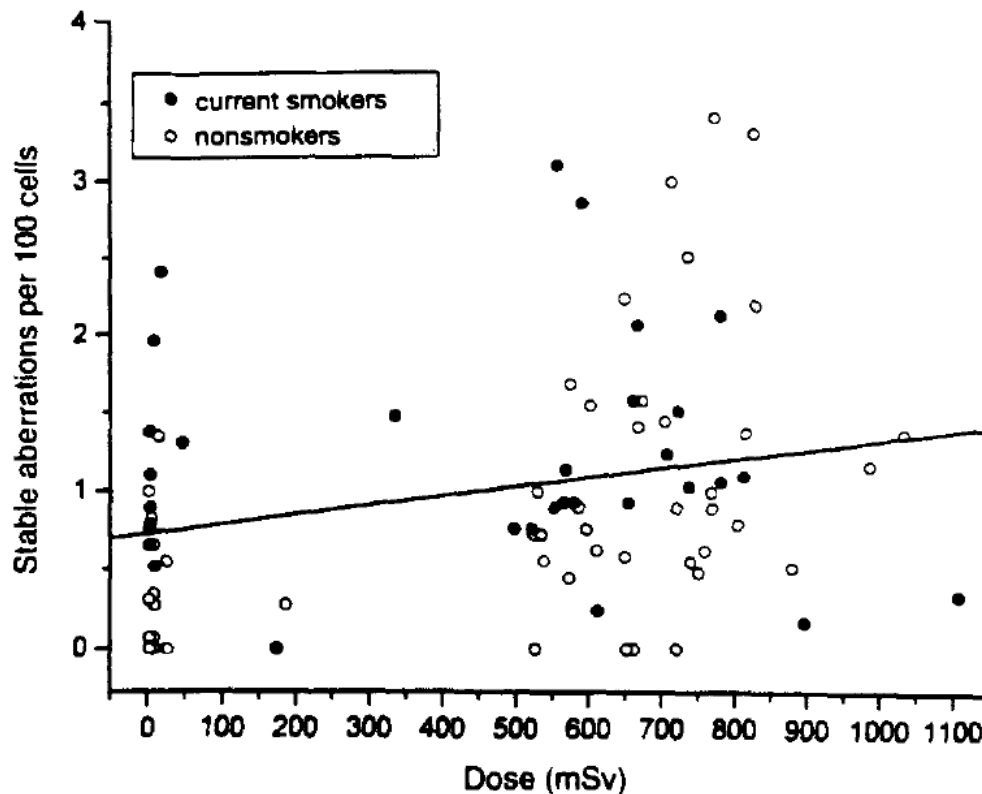
Mortality and Cancer Incidence in the 3rd UK NRRW Analysis 2009

“Within the cohort, mortality and incidence from both leukaemia excluding CLL and the grouping of all malignant neoplasms excluding leukaemia increased to a statistically significant extent with increasing radiation dose. Estimates of the trend in risk with dose were similar to those for the Japanese A-bomb survivors, with 90% confidence intervals that excluded both risks more than 2–3 times greater than the A-bomb values and no raised risk.” Muirhead et al. BMJ 2009



Aberrations (& Leukemia) and DDREF of 6

81 workers, mean ~500 mSv



“The slope of the dose response for stable aberrations is 0.79 aberrations per 100 cells per sievert, which is less than that observed among atomic bomb survivors, and suggests a dose and dose-rate effectiveness factor for chronic exposure of about 6.”

Tucker JD, Tawn EJ, et al. *Rad Res* 148, 1997

Yangjiang County, Guangdong Province,
bordering on South China Sea,
2 regions with thorium-containing monazites







Natural Background Radiation China, Thyroid Nodules

	High Background	Low Background
Number examined	1,001	1,005
Thyroid dose (rad)	14	5
Nodular disease	9.5%	9.3%
RR (95% CI)	1.02 (0.8-1.4)	

Low Dose Rate
External

Wang et al. *JNCI* 82, 1990

Karunagappally Study – Kerala, India

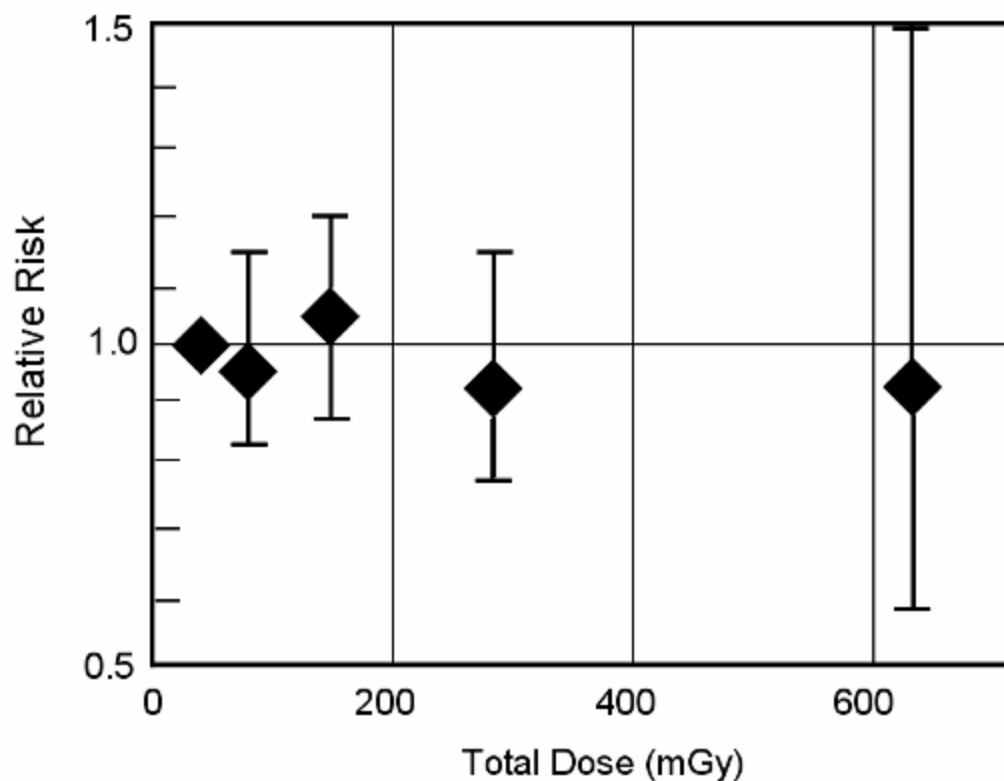


- 400,000 population
- cancer registry, established in 1990
- questionnaire survey of all residents



- radiation measurements in 70,000 homes
- personal dosimetry and biodosimetry
- individual dose estimates (mean, 161 mGy)

Relative Risk of All Cancer Excluding Leukemia by Cumulative Dose to High Background Radiation in Kerala



Nair et al. *Health Physics*, 2009;
Boice et al. *Radiation Research* 2010

Epidemiology has shifted the focus from genetic effects in future generations to somatic effects on the individuals exposed.

Radiation epidemiology (UNSCEAR 2008) tells us that:

- a single exposure can increase your cancer risk for life
- the young are more susceptible than the old
- in-utero susceptibility is no greater than early childhood
- females are more susceptible than males.
- risks differ by organ or tissue and
- some sites have not been convincingly increased after exposure.

Radiation epidemiology has yet to tell us about low dose and low dose rate exposures

The Major Unanswered Question in Radiation Epidemiology

Risk when dose delivered gradually, over long periods of time.

Controversy remains, however, about whether the bomb survivors' brief, onetime exposure would be as harmful if spread over many years. "It's the one major unanswered question," Boice says.

Kaiser J. Radiation Risks Outlined by Bombs, Weapons Work, and Accidents. Science March 25, 2011.

MAJOR RADIATION EVENTS



◀ 1945

Hiroshima-Nagasaki atomic bombs

Population: 94,600 survivor cohort
Health effects: 45% increase in leukemia deaths, 11% increase in solid cancers

1950s

Nevada nuclear tests, U.S.

Population: 160 million U.S. citizens
Health effects: Possible increase in thyroid cancer



1948–72 **Mayak-Techa River, USSR**

Population: 21,000 workers, 30,000 villagers
Health effects: Consistent with A-bomb results

◀ 1979

Three Mile Island, U.S.

Population: 2 million
Health effects: not detected



◀ 1986

Chernobyl, Ukraine, USSR

Population: 5 million in immediate area
Health effects: 6000 thyroid cancers, mainly from contaminated milk

Needed Research When Exposure Spread Over Time

One Million U.S. Radiation Workers and Veterans



- DOE and Manhattan Project workers
- Atomic veterans
- Nuclear utility workers
- Medical & other occupational groups
- Nuclear navy workers





Thank You!

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Preston DL et al. Solid cancer incidence in atomic bomb survivors: 1958-1998. *Radiat Res* 168:1, 2007.

Tubiana M, et al. Dose-effect relationships and the estimation of carcinogenic effects of low doses of ionizing radiation. Joint Report No. 2, Academie Nationale de Medecine, Institut de France-Academie des Sciences, Paris, 2005.

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). UNSCEAR 2006 Report to the General Assembly with Scientific Annexes, Effects of Ionizing Radiation. Vol 1: Report and Annexes A and B. New York: United Nations, 2008; Vol 2: Annexes C, D and E, 2009, 2011